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Comparative Study of Metabolic Effects of Estradiol Benzoate and Testosterone Propionate in Man[1,2,3]

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IN EXTENDING the work of Thorn and Harrop (1) describing the sodium retaining influence of several steroids of the sex hormone series Thorn and Engel (2) noted that the urinary excretion of nitrogen and inorganic phosphorus was depressed by estradiol, estrone or pregnancy urine estrogens. Thus, 5 mg. of estradiol benzoate given in one injection to a normal male dog reduced urinary nitrogen from 10.4 to 8.2 gm. the second day after injection and reduced urinary inorganic phosphorus from 0.56 gm. per day to 0.43 and 0.39 gm. on the second and third days after injection. Urinary sodium and chloride also declined as in the earlier experiments while urinary potassium was unaltered. Evidence was further provided that these effects were not mediated by the adrenal cortex. In adrenalectomized dogs pregnancy urine estrogens partially retarded the diuresis of sodium and chloride, consequent upon withdrawal of adrenal extract. Seventeen mg. of estradiol benzoate given in a single injection to a woman with Addison's disease from whom adrenal extract was withdrawn reduced urinary nitrogen, inorganic phosphorus, sodium and chloride excretion.

From this it would appear that the properties of several androgens in inducing retention of nitrogen and inorganic phosphorus in dogs and man (2–6) may be shared, to some extent at least, by estrogens. Subsequent work, however, has both elaborated and complicated our knowledge of the metabolic properties of estrogens in man. Albright, Bloomberg and Smith (7) examined the effects of estradiol benzoate in women with postmenopausal osteoporosis. As a rule they injected 1.66 mg. intramuscularly every second or third day. In the 3 subjects studied a striking retention of calcium, reaching a maximum of 0.8 to 1.0 gm. per 5-day period and of phosphorus, reaching 0.4 to 0.7 gm. per 5-day period occurred. Estradiol was conceived as repairing defective bone matrix and permitting in consequence the deposit of bone salts. No modification of the rate of bone resorption was

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[2] The testosterone propionate and estradiol benzoate used were generously provided by Dr. Erwin Schwenk and Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J.
[3] An abstract of this paper was read at the 35th Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics, April 4, 1942.

postulated. In contrast to the experience of Thorn and Engel, no distinct evidence of nitrogen retention was obtained in the two subjects studied. In two osteoporotic subjects with Cushing's syndrome, Albright, Parson and Bloomberg (8) found that no retention of calcium, phosphorus or nitrogen was induced by estradiol benzoate, although testosterone propionate, 25 mg. daily, effected conspicuous retention of all 3 substances. The osteoporosis in Cushing's syndrome is conceived by these authors as arising from dissolution of protein matrix under the influence of adrenal cortical hormones. Testosterone propionate was held to repair this matrix, estradiol benzoate not. The variations in calcium metabolism were believed to be secondary to variations in the amounts of calcifiable matrix.

In 5 normal girls, 9 to 13 years old, Johnston (9) observed no evidence of either nitrogen or calcium retention during treatment with theelin given in amounts of 2000 units (rat units or international units?) daily for 6 to 18 days. Indeed, an increase in both urinary and fecal calcium excretion occurred, together with some irregular nitrogen loss. Diethylstilbestrol had a similar effect in another girl. Thus, by virtue either of the types of estrogen used, of the dosage or of the normalcy of the subjects, none of the metabolic effects on nitrogen or calcium metabolism seen by Thorn or Albright and their coworkers could be demonstrated.

From the foregoing, it is clear enough that much more information is needed concerning the metabolic effects of the estrogens in man under a variety of endocrinologic conditions.

In the present account we will describe certain of the metabolic effects of estradiol benzoate when given in 5-mg. (30,000 rat units) amounts daily intramuscularly to 2 eunuchoids, 2 women with ovarian insufficiency, one of whom was masculinized, and one normal woman. In the 2 eunuchoids these effects will be compared with those resulting from 5 mg. daily of testosterone propionate. Supplementary data on the responses of the eunuchoid and the hypogonad woman to larger doses of testosterone propionate are included.

It must be kept in mind that while the smaller amounts of testosterone propionate used (5 mg. daily) fall below replacement requirements, the same amounts of estradiol benzoate substantially exceed such requirements. While such high dosage is useful in dramatizing response in orientation experiments, and is necessary for detailed comparison with the physiologically weaker androgens, application of the data so obtained to the problems of normal ovarian physiology must be made with due reservation.

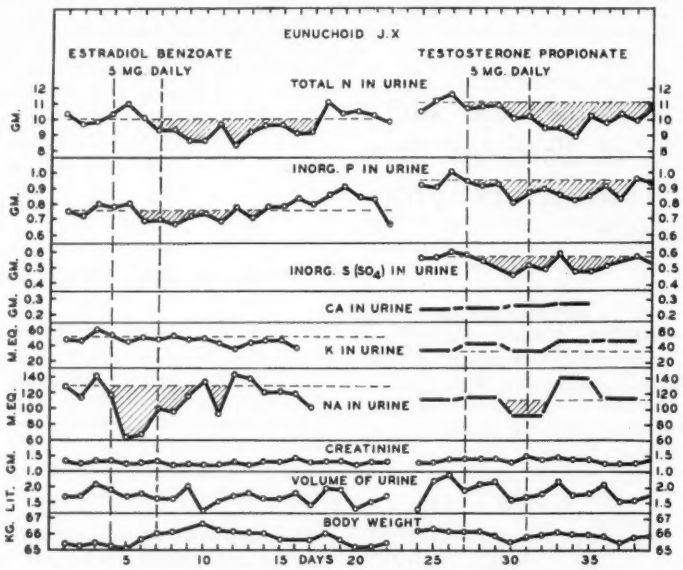

Fig. 1, a and 1, b. Effects of estradiol benzoate and testosterone propionate given intramuscularly on the excretion of several urinary constituents and on the body weight of the eunuchoid *J. X.* The two experiments were not performed consecutively. Interrupted lines designate pretreatment baselines. Shaded areas indicate those changes in values interpreted as significant. Sulfate was determined and is expressed in terms of S.

METHODS

The subjects were given weighed diets containing the same food each day, of sufficient caloric content to permit maintenance of weight, with activity in accordance with the particular individual's desires and capacity. The metabolic and chemical methods used were for the most part described or cited previously (5). Added chemical determinations were inorganic sulfate in urine by the method of Koch (10); total nitrogen in weighed amounts of dried food and feces by the Kjeldahl method as used by us for urine total nitrogen; total phosphorus in food and feces by application of the method for inorganic prosphorus of Fiske and Subbarow (11) to the further diluted ash solution prepared for calcium determinations as below; and calcium in food, feces and urine by the following technique. Appropriate amounts of the dried material were ashed in the muffle furnace at 500–550° C., the ash was extracted with 10 per cent hot hydrochloric acid and the extract made to such volume that 1 to 3 cc. contained 0.1 to 0.3 mg. of calcium. After adjustment of the pH of such samples to 4.2 to 4.4 with ammonium hydroxide using 0.1 per cent bromcresol green as indicator, the calcium content was determined by the technique developed for serum by Kramer and Tisdall, and modified by Clark and Collip (12). The photoelectric colorimeter was used for measurement of the color produced in the determination of creatine and creatinine by the Jaffe alkaline picrate reaction.

In preparation of food for analysis, 50 per cent aliquots of each day's diet were collected in porcelain evaporating dishes for the periods given. The sample for each period was mixed and dried to constant weight at 60 to 65° C., and the residue was then ground and mixed. Feces were collected in glass jars, the respective periods defined by carmine markers. The feces for each period were diluted and thoroughly mixed with an approximately equal weight of water, acidified to bromphenol blue with 10 per cent hydrochloric acid in ethyl alcohol, then dried to constant weight at 60 to 65° C. The residue was ground in a mortar until it could be passed through a 20-mesh sieve.

PROTOCOLS

J.X. (referred by Dr. Carl Moore) was a 28-year-old eunuchoid described in detail previously (5) when an account of his response to 25 and 50 mg. of testosterone propionate daily was given. The experiments described in figures 1, b and 2 were performed in October and December of 1939. He received a diet of C 282, P 68, F 162, Calories 2858, estimated to contain 10.9 gm. of N, 0.887 gm. of S, 1.295 gm. of P, 0.808 gm. of Ca, 1.099 gm. of Na, 1.387 gm. of Cl and 2.767 gm. of K. To this 4 gm. of NaCl was added at the table. The experiment described in figure 1, a was performed in January, 1940. He received a diet of C 294, P 72, F 162, Calories 2922, estimated to contain 11.5 gm. of N, 0.783 gm. of S, 1.265 gm. of P, 0.806 gm. of Ca, 1.198 gm. of Na, 1.543 gm. of Cl and 2.868 gm. of K. To this 4 gm. of NaCl was added at the table. The fluid intake, including distilled drinking water, was 2450 cc. daily throughout all experiments. Before treatment basal metabolic rates of −25 and −27, with basal total Calories for 24 hours of 1315 and 1272 were obtained in December.

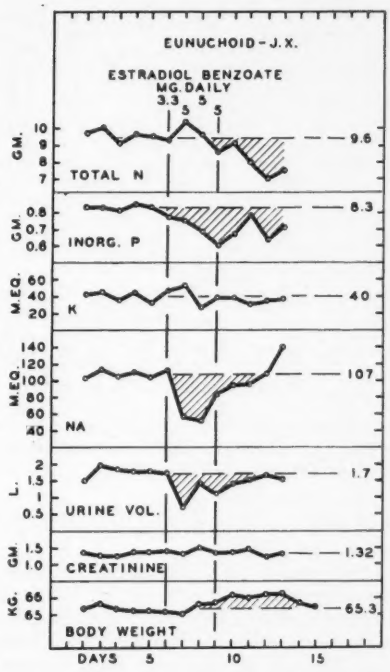

Fig. 2. Effects of estradiol benzoate given intramuscularly on the excretion of several urinary constituents and on the body weight of the eunuchoid *J.X.* Interrupted lines and the corresponding figures on the right designate pretreatment baselines. Shaded areas indicate changes in values interpreted as significant.

J.D. (referred by Dr. I. Becker, University of Illinois) was a 34-year-old eunuchoid studied from September to December, 1941. He was 182 cm. (72.8 in.) tall and weighed 76 kg. (167.2 lb.) at the outset. The span was 183 cm., the sitting height 92.1 cm. The face was smooth, the small amount of facial fuzz being shaved every 2 or 3 weeks, pubic hair was scant, axillary hair somewhat more abundant. Limb and trunk hair was scant. The skin of the trunk and limbs was disfigured by an extensive congenital ichthyosis. The voice was somewhat above average masculine pitch and the laryngeal prominence was not well felt. A considerable prominence of the breast regions was judged after biopsy to be largely adipose tissue without glandular components. The well-formed penis was 1.5 cm. long and .75 cm. thick at the corona. The small well-differentiated scrotum was usually empty but at times two

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE ON THE NITROGEN, PHOSPHORUS AND CALCIUM BALANCES AND ON THE CONCENTRATION OF SEVERAL BLOOD CONSTITUENTS OF THE EUNUCHOID *N.D.*

Day	Total N, gm./day			Total P, gm./day			Ca, gm./day			Plasma		Serum		Body Wt. kg.
	Food	Feces	Urine	Food	Feces	Urine (inorg.)	Food	Feces	Urine	Prot. gm./%	NPN mg. %	P	Ca mg. %	
1														59.6
2										7.12	27	4.3	9.9	59.6
3	11.88	1.32	10.14	0.99	0.40	0.63	0.35	0.37	0.09					
4		**+0.42**			**−0.04**			**−0.12**		7.31	25	4.3	9.3	59.8
5[1]						0.66								59.8
6						0.61					23	4.1	9.4	59.7
7						0.62								59.6
8						0.40				6.91	20	3.8	9.7	59.8
9														60.1
10	11.88	1.25	7.13	0.99	0.37	0.41	0.35	0.38	0.07					60.2
11		**+3.50**			**+0.21**			**−0.09**		6.84	20	3.5	9.1	
12														60.6
13						0.33				6.79	17	3.4	8.9	61.0
14						0.34								61.3
15						0.37				6.56	17	3.6	9.4	
16						0.46								61.6
17						0.52								61.5
18						0.63				6.83	18	4.3	9.3	
19	11.88	1.24	8.21	0.99	0.37	0.64	0.35	0.38	0.06					61.3
20										7.19	21	4.3	9.3	60.6
21		**+2.43**			**−0.02**			**−0.09**						60.8
22										7.04	21	4.3	9.3	60.8

[1] Testosterone propionate, 25 mg. daily intramuscularly, was given from *day 5* to *day 12* inclusive.
Estimated balances are in boldface type.

very small bodies, sensitive to pressure could be felt. The prostate was not palpable.

Roentgenograms of the skull showed a somewhat shallow, but otherwise normal, sella turcica. The fundi and visual fields were normal. Epiphyses of the shoulder girdle, elbow, and hand were all fused with their respective diaphyses. Those of the iliac crests were, however, still unfused, this delay of some 14 years constituting the only evidence of retarded epiphyseal fusion. An oral glucose tolerance test showed a flat curve, the blood-sugar values ranging from 72 to 88 mg. per cent, but an intravenous glucose tolerance test was normal. An intravenous insulin tolerance test (0.1 U of insulin/kg. = 7.6 U of insulin) produced hypoglycemia (29 mg.%) at .5 hour with symptoms, but the return to approximately baseline values at 2 hours (80 mg.%) was normal.

TABLE 2. EFFECT OF ESTRADIOL BENZOATE ON THE CONCENTRATION OF BLOOD-UREA NITROGEN, SERUM INORGANIC PHOSPHORUS AND HEMATOCRIT OF THE EUNUCHOID *J.D.*

Day[1]	Blood Urea N, mg. %	Serum Inorganic P, mg. %	Hematocrit, vol./100 cc.
x	10.8	4.1	41
y	10.3	4.7	44
5[2]	12.0	4.2	43
7	10.6	3.9	43
9	8.1	3.9	41
12	8.3	3.9	41
14	9.4	4.3	42
19	9.3	3.8	43
21	10.7	4.2	42
26[3]	10.1	4.1	40
28	7.7	4.1	39
34	8.8	4.3	42

[1] *Days x* and *y* control days preceding enumeration as given in figure 3.
[2] Estradiol benzoate intramuscularly 5 mg. daily *days 5 to 9* inclusive.
[3] Testosterone propionate intramuscularly 5 mg. daily *days 25 to 34* inclusive.

Assays for 17-ketosteroids, colorimetric as by Holtorf and Koch,[4] gave a value of 18.1 mg. per day for a 6-day collection. By capon-comb assay only 1 to 3 international units per day could be detected. Thus, although a normal amount of color-yielding material was present, only a small fraction of this was androgenic. The precise amount of urinary gonadotropins (mouse uterine method) was not determined although Dr. Varney found more than 30 mouse units excreted per day. Thus, normal amounts at least were present and no evidence accordingly is adduced that the hypogonadism was primarily of pituitary origin.

In conclusion *J.D.* was a eunuchoid suffering presumably from primary testicular insufficiency of unknown origin.

The data shown in figure 3 and table 2 were acquired while the subject was on a constant diet of C 306, P 85, F 136, Calories 2788. This was estimated to contain 1.080 gm. of S, 1.196 gm. of Na, 1.756 gm. of Cl and 4.552 gm. of K. By analysis it contained 14.6 gm. of N, 1.29 gm. of P, and 0.77 gm. of Ca per day. To this, 4 gm. of

[4] The assays for 17-ketosteroids were made by Mr. Paul Munson and Mr. Carter Johnston in the Department of Biochemistry.

NaCl was added at the table. Fluid intake, including distilled drinking water, was kept constant at 2800 cc. per day. Creatine, 1.32 gm., was ingested daily at breakfast beginning 4 days before treatment with estradiol benzoate.

The data shown in figure 4 and table 3 were acquired while the subject was on a diet of C 296, P 86, F 122, Calories 2626. This was estimated to contain 1.027 gm. of S, 1.091 gm. of Na, and 3.516 gm. of K. By analysis it contained 15.2 to 15.4 gm. of N, 1.28 to 1.36 gm. of P, and 0.73 to 0.77 gm. of Ca. Four gm. of NaCl was added daily at the table. Fluid intake, including distilled drinking water, was kept at 2500 cc. daily. Creatine, 1.32 gm., was ingested daily throughout the experiment.

The data given in figure 3 do not include values for basal heat production during the experiments with 5 mg. of estradiol benzoate and 5 mg. of testosterone propionate daily. The range was from −14 to −21, 1464 to 1595 Calories per 24 hours without any variation attributable to the treatment used. After the conclusion of the period of treatment with 5 mg. of testosterone daily shown in figure 3, 25 mg. of testosterone propionate was given daily for 5 days without further effect on the creatinuria. Thirteen days after discontinuing the androgen the experiment shown in figure 4 and table 3 was begun.

N.D. was a 34-year-old eunuchoid, in whom both the clinical features and metabolic response to testosterone propionate, 25 mg. daily, have been described (4). He was re-studied in February, 1940, having been untreated for 9 months. The metabolic data are given in table 1. At this time his diet comprised C 269, P 64, F 107, Calories 2295. By analysis this provided 11.88 gm. of N, 0.99 gm. of P and 0.351 gm. of Ca. Four gm. of sodium chloride was added at the table and a constant fluid intake, including distilled drinking water, and amounting to 2250 cc. daily was provided. The basal metabolic rates before treatment were −18 and −19 and 1329 and 1311 total Calories per 24 hours.

A.B. (referred by Dr. Sara Janson) was an 18-year-old girl who was short (147 cm., 4 ft. 9.5 in.) and had scant pubic and axillary hair, flat breasts, juvenile genitalia and primary amenorrhea. The urinary gonadotropins were 250 and 400 to 450 mouse units per day. values equal to those of the castrated or menopausal woman. She has been fully described as a member of an interesting group of hypogonad women (13). The metabolic studies were made in April and May of 1940 and are illustrated in figure 5 and table 4. At this time she ate a diet of C 218, P 42, F 85, Calories 1805, estimated to contain 6.72 gm.

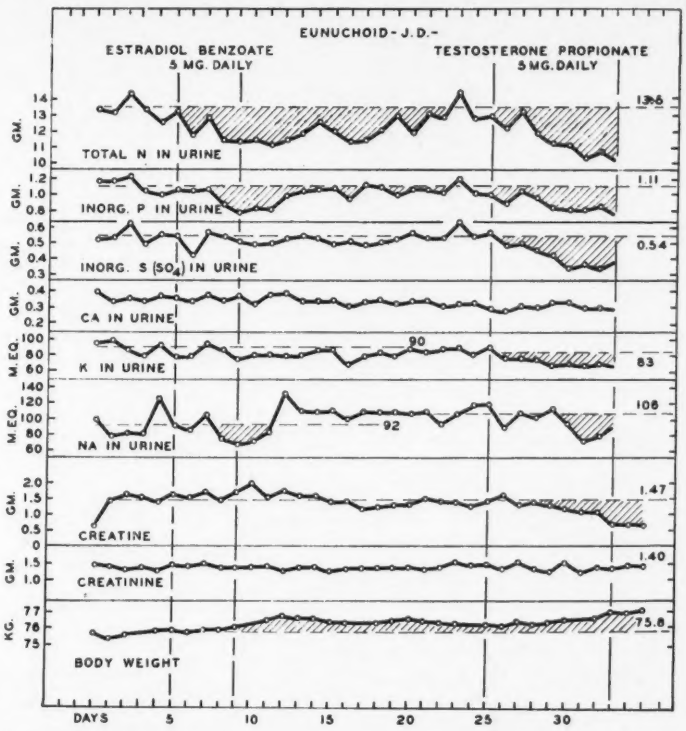

Fig. 3. Effects of estradiol benzoate and testosterone propionate, given intramuscularly, on the excretion of several urinary constituents and on the body weight of the eunuchoid *J. D.* Interrupted lines and the corresponding figures on the right designate pretreatment baselines. Shaded areas indicate changes in values interpreted as significant. Sulfate was determined and is expressed in terms of S. Creatine hydrate, 1.32 gm. daily, by mouth.

TABLE 3. EFFECT OF ESTRADIOL BENZOATE ON THE NITROGEN, PHOSPHORUS AND CALCIUM BALANCES AND ON THE CONCENTRATION OF SEVERAL BLOOD CONSTITUENTS OF THE EUNUCHOID *J.D.*

Days	Total N, gm./day			Total P, gm./day			Calcium, gm./day			Blood	Plasma		Serum			Hematocrit, vol./100 cc.
	Food	Feces	Urine	Food	Feces	Urine (inorg.)	Food	Feces	Urine	Urea N mg. %	Prot. gm. %	NPN mg. %	P mg. %	Ca mg. %	Na mm/l.	
3 4 5 6	15.40	1.85 **−0.24**	13.79	1.35	0.30 **+0.03**	1.02	0.77	0.40 **+0.13**	0.23	13.4	7.42	21	4.2	9.7	145	44
7[1] 8 9 10	15.24	1.84 **+0.32**	13.08	1.28	0.33 **−0.02**	0.97	0.73	0.43 **+0.10**	0.20	9.9 9.3	7.27 7.16	21 17	3.7 3.7	9.5 8.3	144 143	45 45
11 12 13 14	15.78	1.68 **+1.76**	12.34	1.36	0.29 **+0.22**	0.86	0.73	0.37 **+0.13**	0.24	9.2	6.89	17	3.9	9.2		43

[1] Estradiol benzoate, 5 mg. daily intramuscularly, from day 7 on.
Balances in boldface type.

of N, 0.597 gm. of S, 0.810 gm. of P, 0.617 gm. of Na, 0.916 gm. of Cl, and 2.152 gm. of K. Four gm. of NaCl was added daily at the table. The fluid intake, including distilled drinking water, was kept constant at 1920 cc. daily. Basal metabolic rates before treatment ranged from −10 to −14, and from 1020 to 968 total Calories per 24 hours.

R.F. (referred by Dr. I. Becker) was a 26-year-old woman who was short (141 cm., 4 ft. 7 in.) and had scant pubic and axillary hair, hypoplastic breasts and genitalia and primary amenorrhea. The urinary gonadotropins, like those of *A.B.*, were high, ranging between 250 to 350 mouse units per day. She likewise has been fully described (13). The metabolic studies reported here were performed in November, 1940, and are illustrated in figure 6. At this time she ate a diet of C 263, P 56, F 92, Calories 2104, estimated to contain 8.96 gm. of N, 0.70 gm. of S, 0.93 gm. of P, 0.87 gm. of Na, 0.91 gm. of Cl, and 2.74 gm. of K. Five grams of NaCl was added at the table. Fluid intake, including distilled drinking water, was kept constant at 2200 cc. daily. The basal metabolic rate, after training ranged from −6 to −8, the basal total Calories per 24 hours, from 1025 to 1053.

TABLE 4. BLOOD CONSTITUENTS OF *A.B.* DURING TREATMENT WITH ESTRADIOL BENZOATE

Day	Blood Urea N mg./100 cc.	Serum Inorg. P mg./100 cc.	Serum Na m.m./l.	Serum K m.m./l	Hematocrit vol. %
6[1]	7.3	4.4	135.7	4.56	42
7	8.1	4.5	137.6	4.50	42
9	10.0	4.9	136.6	4.48	42
10	8.7	4.6	137.2	4.50	39
14	9.5	4.7	139.1	4.76	41
17[2]	7.3	4.0	133.8	4.70	40
21	5.2	3.7	142.5	4.66	39
23	5.5	3.9	142.8	4.78	41 (day 24)
27	5.8	4.0	140.8	4.57	41 (day 28)
30	7.1	4.1	138.1	4.61	41
35	7.5	4.5	139.4	4.61	42 (day 36)

[1] Progesterone 15 mg. daily, *days* 6, 7, 8 and 23, 24, 25.
[2] Estradiol benzoate, 5 mg. daily, *days* 15–25 inclusive.

V.F. was a 20-year-old masculinized girl with ovarian insufficient. She was short (144 cm., 4 ft. 8 in.) with a relatively long trunk (81 cm. sitting height). The span (143 cm.) bore the usual relation to stature. The patient's musculature was sturdy, her manner direct, with a suggestion of masculinity. Her tastes were feminine. Little or no sexual desire was recognized. She had never menstruated. The body hair was abundant and of masculine

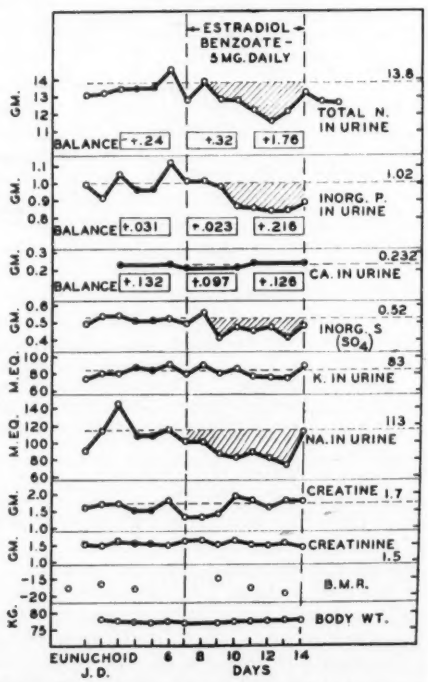

Fig. 4. EFFECTS OF ESTRADIOL BENZOATE given intramuscularly on the excretion of several urinary constituents and on the basal metabolic rate and body weight of the eunuchoid *J.D.* Interrupted lines and the corresponding figures on the right designate pretreatment baselines. Shaded areas indicate changes in values interpreted as significant. Blocks summarize the balances detailed in table 3. Sulfate was determined and is expressed in terms of S. Creatine hydrate, 1.32 gm. daily by mouth.

distribution with a moderate excess of unpigmented slightly coarse hair on the face. The voice was deep. Mammary areas bore small nipples and no palpable breast tissue. The clitoris was 2 cm. long with a well defined glans and no prepuce. The labia majora were not prominent and contained no gonadal inclusions. The urethra opened into the vulva. Benath the urethra was a narrow vaginal opening admitting a little finger. A cord-like structure occupied the uterine position on rectal examination. No prostatic tissue could be felt. Neither gonad could be palpated. Seven years previously Dr. T. G. Amos of Detroit had explored the abdomen. Small ovaries obtained less than 10 mouse-utrine units of gonadotropic material per day in a 3-day collection.

The data shown in figure 7 were obtained in June and July, 1941. She consumed at this time a diet of C 235, P 54, F 82, Calories 1894; containing an estimated 8.64 gm. of N, 0.65 gm. of S, 1.16 gm. of P, 1.10 gm. of Ca, 0.976 gm. of Na, 1.53 gm. of Cl and 3.08 gm. of K. She received, in addition, 4 gm. of NaCl added at the table. Because of the warmth of the weather variation was allowed in the amounts of distilled drinking water, the total fluid intake varying accordingly from 1650 to 2600 cc. It was constant at 1900 cc. from *day 1* through *day 10*

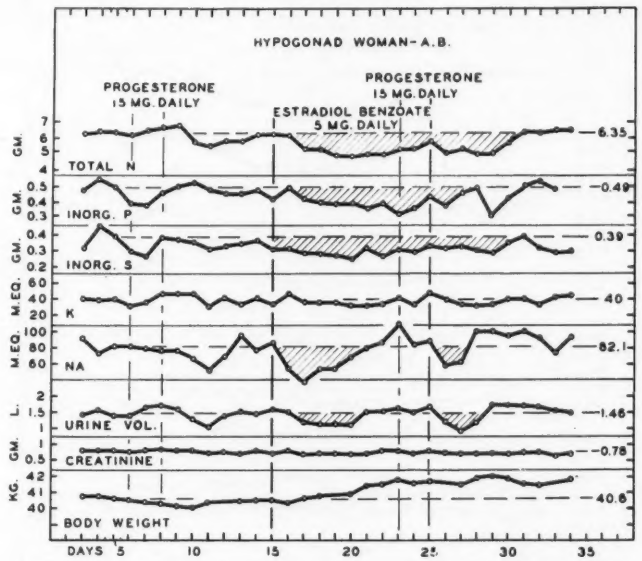

Fig. 5. THE EFFECTS OF ESTRADIOL BENZOATE given intramuscularly on several urinary constituents and body weight of the short hypogonad girl *A. B.* Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant. Sulphate was determined and is expressed in terms of S.

and uterus were found in the normal position. No tumor masses were found in either adrenal. Biopsy specimens of each ovary showed numerous follicles largely undeveloped. Since pyelograms gave no evidence of kidney displacement at the present time the abdomen was not again opened.

The sella turcica was normal on roentgen-ray examination. The epiphyseal cartilages of the hand, shoulder, knee and pelvis were all ossified, indeed roentgenograms of the elbow and knee at 13 years of age showed fusion of epiphyses (Dr. Amos). The pelvis was interpreted as generally contracted.

Colorimetric measurements of urinary 17-ketosteroids[4] gave a value of 61.0 mg. per day (5-day sample). By capon assay, 54 I.U. of androgenic activity were excreted per day. One year previously a 6-day collection had shown 122 mg. per day with a very high androgen assay (capon's comb) of 385 I.U. per day. The equivalent of 5 micrograms of estrone was present in both specimens. Dr. Varney

(fig. 7) and at 2100 cc. from *day 15* to the end. The basal heat production ranged from ±0 to +1 and from 1193 to 1202 total Calories per 24 hours before treatment.

The concentration of several blood constituents was unaltered by treatment with estradiol benzoate. These may be noted as follows: plasma proteins 6.20 to 7.01 gm. per 100 cc.; plasma non-protein N 19 to 22 mg. per 100 cc., serum Ca 8.9 to 9.4 mg. per 100 cc.; P 4.1 to 4.4 mg. per 100 cc., Na 134.2 to 142.1 m.eq. per liter; Cl 98.4 to 102.6 m.eq. per liter and K 4.18 to 4.59 m.eq. per liter.

The estradiol benzoate had no effect on breast buds and produced no bleeding from the uterus on withdrawal of treatment. She later developed breast tissue during treatment with diethylstilbestrol while under the cae of Dr. M. E. Davis.

B.S. was a normal 19-year-old girl with regular menses occurring every 25 to 27 days and lasting 3 days. Pain

was present on occasion during the first day. The experiment illustrated in figure 8 was performed in April and May, 1941. Estradiol benzoate was started on the 16th day of the menstrual cycle. She mensturated normally the 3rd day after stopping treatment, providing an interval of normal length. The diet comprised C 280, P 59, F 95, Calories 2211; and was estimated to contain 9.44 gm. of N, .075 gm. of S, 1.13 gm. of P, 1.04 gm. of Na, 1.44 gm. of Cl and 2.80 gm. of K. To this 4 gm. of NaCl was added at the table. The fluid intake, including distilled drinking water, was kept constant at 2000 cc. daily. The basal metabolic rate ranged from −5 to −9 and from 1307 to 1255 total Calories per 24 hours.

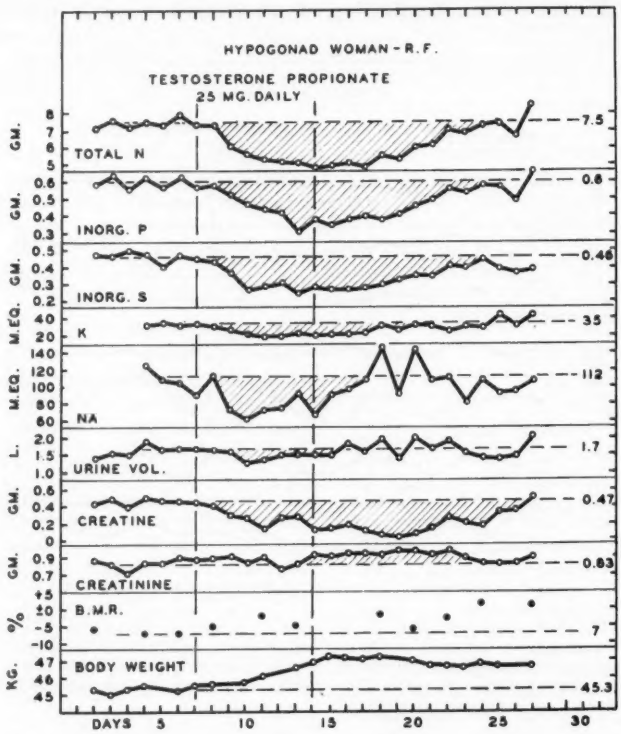

Fig. 6. Effects of testosterone propionate given intramuscularly on several urinary constituents, basal metabolic rate and body weight of the short hypogonad girl *R. F.* Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant. Sulphate was determined and expressed as S.

DISCUSSION

Many of the characteristic metabolic effects of testosterone propionate may be obtained in the eunuchoid with as little as 5 mg. daily intramuscularly. Thus in *J.K.* (cited by Sandiford, Knowlton and Kenyon, 14, fig. 2) a decline in urinary nitrogen of 3.04 gm. per day at the time of maximum influence, occurred with 5 mg. of the androgen as compared to a decline of 6.40 gm. per day with 25 mg. of testosterone propionate daily. Since 50 mg. of testosterone propionate had no more effect than 25 mg. nearly half of the possible androgen influence on nitrogen metabolism was obtained with the small dose of 5 mg. daily. *J.X.* (fig. 1, b) further illustrates the same point. At the time of maximum effect of 5 mg. of testosterone propionate, a decline in urinary nitrogen of 1.8 gm. per day occurred. In a previous experiment (4) 25 mg. produced a decline of 3.3 gm. per day in this subject. A similar distinct reduction in urinary nitrogen of at least 3.0 gm. per day is shown in the eunuchoid *J. D.* (fig. 3) with the small dose. Urinary inorganic phosphorus was reduced by 5 mg. of testosterone daily in both *J. X.* and *J. D.*, as was urinary sodium. Urinary potassium was reduced in *J. D.* and was unaffected in *J. X.* Urinary inorganic sulfate was decisively reduced in both. No change was produced in the urinary calcium of either subject. This last was to be expected since neither urinary nor fecal calcium excretion was affected in an experiment of this dura-

tion in the eunuchoid *N. D.* who received 25 mg. of testosterone propionate daily (table 1). The creatinuria induced in *J. D.* by oral administration of creatine was reduced materially by 5 mg. of testosterone propionate daily. It is of passing interest that this creatinuria was not further modified by the subsequent administration of 25 mg. of testosterone propionate daily. The elevation of basal heat production in *J. D.* during this experiment was insignificant, but we have already pointed out that even with heavier dosage considerable time may often elapse before notable increase in heat production occurs (14).

The sensitivity of the eunuchoid to the metabolic effects of small amounts of testosterone propionate is duplicated in the growing boy (15) and is accordingly of considerable biologic interest. We have previously discussed our reasons for believing that the androgens exert an important, even though insufficiently defined, somatotropic influence (4, 5). Many of the metabolic phenomena described here and elsewhere appear to be the chemical manifestations of tissue growth, exemplified by the progressive gains in height and weight of undergrown, underdeveloped boys treated with testosterone propionate (16, 17, 18) methyl testosterone (19, 20) and chorionic gonadotropins (21, 22). It is likely, therefore, that the testicular hormone makes a physiological contribution to the masculine adolescent growth spurt. Since the small amounts of androgens necessary to initiate metabolic response seem to fall below those required for conspicuous evolution of most secondary sex characters, the testicular contribution to adolescent growth may begin relatively early, before secondary sex characters are well advanced. An examination of Richey's data (23, figures 5 and 6, p. 30 and 31) shows that the normal pubertal growth increment is apparent more than 2 years before the advent of axillary hair.

The metabolic effects of 5 mg. of estradiol benzoate daily in the eunuchoid resemble those of a comparable amount of testosterone propionate in several respects. There is a general agreement with the findings of Thorn and Engel in the normal male dog and in the woman with Addison's disease (2). The data are given in figures 1, a and 2 for *J. X.* and in figures 3 and 4 and tables 2 and 3 for *J. D.* There was a decline in urinary nitrogen, fairly well defined by the fourth day of treatment, reaching a maximum by the fourth to the eighth day, and sustained often with some irregularity for 10 to 12 days after cessation of the injections. As is often the case with testosterone propionate in the eunuchoid, no evidence of a compensatory loss of urinary nitrogen was obtained during the recovery period. The degree of decline approximated that obtained with 5 mg. of testosterone propionate in the same patients. Fecal nitrogen was unaltered (table 3) and the concentration of several nitrogenous

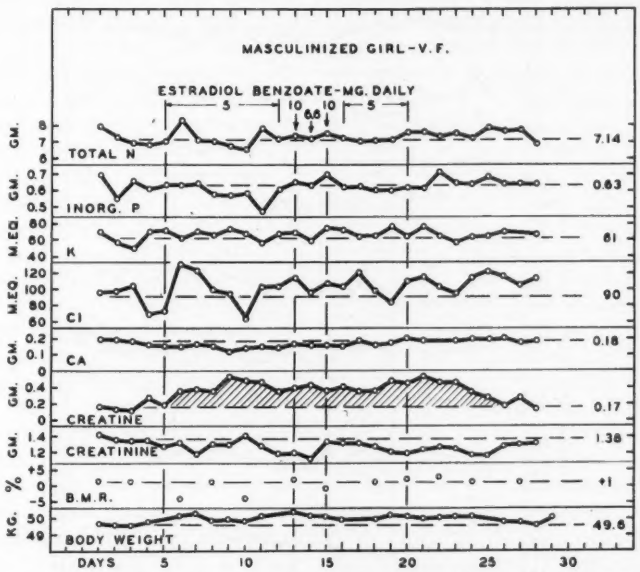

Fig. 7. Effects of estradiol benzoate given intramuscularly on several urinary constituents, basal metabolic rate and body weight of the masculinized girl *V. F.* (adreno-genital syndrome). Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant.

constituents of the blood—blood urea, plasma protein and non-protein nitrogen—was not increased (table 3). In these respects also the response was similar to that characteristic of testosterone propionate (table 1).

As with testosterone propionate, the point of deposit of the retained nitrogen is obscure. Expansion of the extravascular, extracellular fluid compartment of the body even to the full extent of the weight gained would account for only a minute fraction of the nitrogen retained (0.14 gm. in *J. D., experiment 1*). Presumably protein is deposited somewhere and there is now no evidence permitting decision as to whether the locus is the same as with testosterone propionate or not. Obviously, growth of internal female genitalia is not essential for the phenomen. As with testosterone propionate (4) the amount of body weight gain attributable to retention of protein, with associated water in skeletal or visceral tissue, falls short of accounting for the actual weight gain (300 gm. at *day 11*, in *J. D.*, fig. 3 as compared to 800 gm. of actual gain). Furthermore, weight is commonly lost while nitrogen retention is still proceeding after cessation of treatment. Water retained with sodium and chloride is therefore in all probability largely responsible for the weight increment in brief experiments with estradiol benzoate, just as it is with testosterone propionate.

Urinary inorganic phosphorus consistently declined under the influence of the estrogen in all 4 experiments in the 2 eunuchoids. Fecal phosphorus was unaffected and the concentration of inorganic phosphorus in the serum was not increased (tables 2, 3). Neither urinary nor fecal calcium nor the calcium content of the serum were affected (figs. 3, 4, table 3). These reactions were similar qualitatively and quantitatively to the response to testosterone propionate (fig. 1, b, 3; tables 1, 2, 3). While the influence of estradiol benzoate on inorganic phosphorus metabolism in these subjects is in agreement with the results of Thorn and Engel on the normal male dog and the woman with Addison's disease, and those of Albright, Bloomberg and Smith in women with osteoporosis, the latter group demonstrated notable cal-

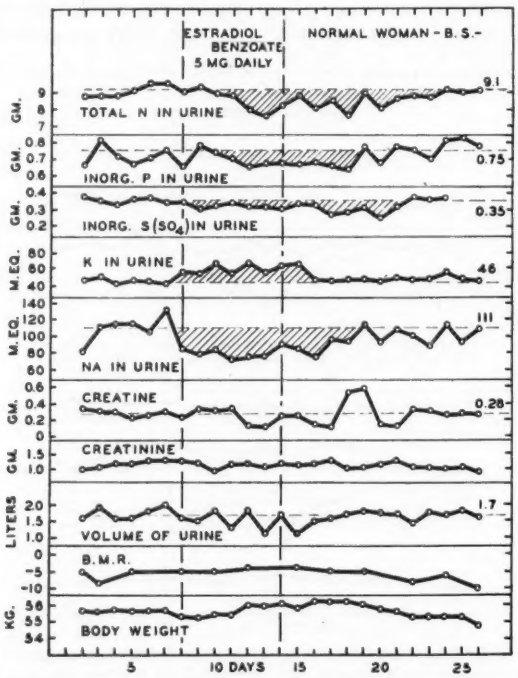

Fig. 8. Effects of estradiol benzoate given intramuscularly on several urinary constituents, basal metabolic rate and body weight of the normal young woman *B. S.* Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant. Sulfate was determined and is expressed in terms of S.

cium retention in their subjects. Either the osteoporotic women were especially sensitive to the calcium-retaining properties of estradiol benzoate or the length of our periods of treatment was insufficient to develop this effect, despite our substantially heavier dosage. Since the maximum calcium retention in the women with osteoporosis occurred at about 20 days, more protracted study of the eunuchoid is obviously necessary. Within the limits of our experimental periods, however, retention of inorganic phosphorus seems more likely to be correlated with that of nitrogen than with that of calcium.

In *J. D.* (fig. 4) urinary sulfate declined during treatment with estradiol benzoate. This was not as conspicuous however as with the same dose of testosterone propionate (fig. 3) and was hardly apparent in the other experiment on this same subject (fig. 3).

The consistent sharp decline in urinary sodium excretion in all 4 experiments on the eunuchoids is in agreement with the repeated demonstration by Thorn and his coworkers of the sodium-retaining action of estradiol in both dogs and man (1, 2, 24). As in the experiments with testosterone propionate, sodium diuresis occurs in the early phases of the recovery period while nitrogen retention is still going on. While the extent of the decline in urinary sodium excretion may somewhat exceed that induced by testosterone propionate (*J. X.*) the difference is not as great as in the dog in which testosterone has little or no sodium-retaining action (2).

Urinary potassium excretion is judged uninfluenced by the estrogen. In *J. D.* (fig. 3) the initial baseline is probably too high by virtue of two values at the beginning of the experiment, and the comparison of the treatment period with the recovery baseline indicates no decisive influence. This is in agreement with the results of the other three experiments (*J. X.*, fig. 1, a, 2; *J. D.*, fig. 4). Five mg. of testosterone propionate may (*J. D.*, fig. 3) or may not (*J. X.*, fig. 1, b) reduce urinary potassium excretion. This response is usually distinct with 25 mg. daily.

An increase of 1 to 1.5 kg. in body weight may occur as a result of treatment with estradiol benzoate (*J. X.*, fig. 1, a, 2; *J. D.*, fig. 3) or may not be apparent (*J. D.*, fig. 4). This gain in weight must be due largely to water retention, presumably chiefly in association with retained salt, as previously noted. In some experiments (*J. X.*, fig. 2) urine volume is sharply reduced during treatment to rise thereafter, in others (*J. X.*, fig. 1, a) the variations in urine volume are less satisfactory, presumably because uncontrolled forces modifying water metabolism exert complicating influences.

When creatinuria was sustained at high levels by creatine ingestion in *J. D.* no reduction in the amount excreted was obtained when estradiol benzoate was given (fig. 3, 4). This is in distinct contrast to the depression of exogenous creatine excretion by 5-mg. doses of testosterone propionate (fig. 3). Jailer's experience (25) in the male monkey was similar, although the amount of this estrogen (100 R.U., 0.017 mg.) was not as large as that of the androgen (2–5 mg.). Kun and Peczinek (27) likewise describe the creatinuria of the castrated male rat as reduced by 'proviron' but not by 'progynon,' and Schittenhelm and Bühler (28) suggest the same difference in the hypogonad human male receiving small amounts of the sex hormones orally. At first thought one is inclined to relate reduction of creatinuria to an improvement in the metabolism of muscle and to suppose accordingly that testosterone has an advantage over estradiol in this regard. Such a supposition would be in agreement with the observation of Papanicolaou and Falk (26) that testosterone propionate, but not urinary estrogens ('amniotin') would induce hypertrophy of the stemporal muscle of the castrated male or normal female guinea-pig. While this interpretation may be correct, recent studies of Wilkins, Fleischmann and Howard (20) indicate that the effects of androgens on creatine metabolism are more complex than they first appeared to be. In underdeveloped dwarfish boys retaining nitrogen and growing under the influence of oral methyl testosterone, creatine excretion on a creatine-free diet substantially increased in time. The question arises as to whether the enhanced creatinuria in their subjects, in which there was every reason to suppose a characteristic metabolic effect of androgens, was due to the use of methyl testosterone rather than testosterone propionate. Until this matter is settled by experiment, we do not feel that we can force the concept of obligatory association between the effects of androgens on muscle and reduction in excretion of ingested creatine.

No distinct effect on basal heat production was induced by estradiol benzoate in the eunuchoid *J. D.* but small amounts of testosterone propionate likewise fail to make much difference in the relatively brief periods studied here.

The effects of 5 mg. of estradiol benzoate, daily, in the sexually underdeveloped short girl, *A. B.*, resemble very closely those in the eunuchoids. Urinary nitrogen, inorganic phosphorus and sodium excretion were depressed, the last temporarily, while potassium excretion was unaffected (fig. 5). Sulfate excretion was probably depressed, but the return to the baseline during recovery was insufficiently decisive. There was no change in the concentration of serum sodium, potassium, inorganic phosphorus or packed red cells. A slight depression in concentration of blood urea nitrogen is suggested (table 4). The data on the effects of progesterone charted will not be discussed as we

have not as yet secured repeatable metabolic effects in man with this steroid.

A. B. belongs to the group of dwarfish, sexually immature women with high urinary gonadotropin titers described recently by Varney, Kenyon and Koch (13) and by Albright, Smith and Fraser (32). It is of interest that her capacity to retain nitrogen was excellent, despite her moderate limitation of growth. In a second individual of this type (*R. F.*) testosterone propionate, 25 mg. daily, intramuscularly, is seen to exert its characteristic metabolic effect (fig. 6).

When ovarian insufficiency, however, is accompanied by evidences of gross masculinization, estradiol benzoate may exert little or none of its usual action. *V. F.* was a masculinized girl of 20 with enlarged clitoris, hypoplastic breasts and uterus, amenorrhea, deep voice, masculine hair distribution, firm, well-developed musculature and short stature due to premature ossification of epiphyseal cartilages of the long bones. At this time she excreted 61 mg. of 17-ketosteroid material per day (colorimetric) and 50 I.U. of estrone equivalents per day. Previous surgical exploration, with biopsies of both ovaries showed ovarian tissue present but had not demonstrated an adrenal tumor. It is likely, however, that her adrenals were the source of the excessive androgens. *V. F.* (fig. 7) gave no distinct evidence of response in urinary nitrogen, inorganic phosphorus or chloride to estradiol benzoate even when the dose was elevated to 26.6 mg. in 3 days. The concentration of several blood constituents was unaltered (see protocols). There was no growth of breast tissue in the 16 days of treatment with the estrogen, nor was there any withdrawal bleeding thereafter, this subject contrasting in both respects with *A. B.* It may be inferred that *V. F.*'s indigenous hormones interfered with metabolic response to estradiol benzoate. This interference could be by some direct or indirect endocrine mechanism, or simply by virtue of exerting metabolic influence to the limit of the organism's capacity for response. The suppression of estrogen effect was not complete however in all respects. Diethylstilbestrol, 1 mg. daily in the hands of our colleague Dr. M. E. Davis eventually induced substantial growth of breast buds in this girl.

The increase in urinary creatine during the course of estradiol benzoate treatment in *V. F.* constitutes an, as yet, isolated observation. It was certainly not apparent in the study of the normal woman *B. S.* Urinary creatinine in *V. F.* may have been irregularly decreased at this time, although one naturally hesitates to rely too much on minor changes in creatinine excretion. This phenomenon of heightened creatinuria requires confirmation and further study before speculations as to its mechanism can be usefully entertained.

The effects of 5 mg. of estradiol benzoate daily were studied in a normal young woman (*B. S.*, fig. 8) in the interval between menstrual periods. Characteristic reduction in urinary excretion of nitrogen and inorganic phosphorus was induced. Urinary inorganic sulfate declined slightly. Sodium and chloride excretion declined, effects more likely due to the large amount of added estrogens than to the smaller amounts of endogenous hormones. The well-defined rise in urinary potassium excretion in this subject is anomalous. We have not seen it elsewhere, but hesitate to regard it yet as characteristic of the normal woman. The increase in body weight seems distinct. There was no change in basal heat production. Creatine and creatinine excretion in the urine were judged unaffected. There is accordingly no evidence that normal feminine hormones modify the reaction of the organism to estradiol benzoate, if one excepts the curious data on urinary potassium excretion. We have previously noted that the normal young woman either might give the usual metabolic response to 25 mg. of testosterone propionate daily or might respond indistinctly in several respects (5). Urinary potassium showed no exceptional behavior in this earlier work.

It may be concluded that estradiol benzoate, when administered in sufficient amounts to sexually underdeveloped men, to sexually underdeveloped women with little or no maturation of secondary sex characters and to normal women shares several of the metabolic properties of testosterone propionate. Retention of nitrogen, inorganic phosphorus and sodium may be induced with either substance. In other respects some differences may exist. Urinary potassium excretion was not affected by 5 mg. of estradiol benzoate daily save in the normal woman in whom it was increased. Testosterone propionate always reduces urinary potassium as far as we know, if it affects it at all, but this influence may not always be apparent with 5 mg. daily. While urinary sulfate was not always conclusively depressed by estradiol benzoate, there are sufficient suggestions of this effect to exclude emphasis on this point as a decisive distinction. No evidences of increased heat production due to estradiol benzoate have been secured, but 5 mg. of testosterone propionate daily will often not increase heat production in relatively brief periods of treatment. Creatinuria, when sustained at high levels by creatine ingestion in the eunuchoid, was not depresed by estradiol benzoate as it was by testosterone propionate. Tentatively, this seems a valid distinction between the properties of these two substances but it cannot serve as yet to differentiate the metabolic effect of the estrogen from that of all androgens. As previously noted, methyl testosterone given orally will enhance creatinuria in undergrown underdeveloped boys (20). Thus, none of the metabolic effects of

androgens demonstrable in hypogonad individuals can as yet be held to be consistently and exclusively associated with the androgenicity of these steroids.

Both in this paper, and elsewhere, we have attempted to relate the anabolic effects of the androgens in man to processes of somatic tissue growth. Unfortunately, the term 'somatotropic' which we have used, must still be used loosely as the sites of new tissue deposit in man are difficult to ascertain precisely. The question now arises as to whether the somewhat similar metabolic properties of the estrogens justify the hypothesis that the ovary as well as the testis exerts an anabolic influence on non-genital tissues in man. Albright, Bloomberg and Smith (8) have already suggested such an anabolic action of the estrogens on the bone matrix of osteoporotic women, accounting thus secondarily for the retention of calcium and phosphorus induced. The data given here for the eunuchoid make it sufficiently clear that growth of female genitalia does not solely determine the retention of such constituents of tissue as nitrogen and phosphorus. It is thus well within the realm of possibility that the estrogens normally exert a somatotropic influence during the growth period in man. Sufficient attention has not as yet been given replacement doses of the estrogens, however, to permit judgment as to the likelihood of such an influence. The amounts of androgens which exhibit anabolic effects are small in physiologic terms. The corresponding amounts of estrogens are grossly above physiologic levels. W. M. Allen (29) has estimated that only 5 mg. of estradiol benzoate given over 3 weeks of time are necessary to prepare the uterus of the castrated woman for withdrawal bleeding. This is about one-twentieth of our dosage. The careful studies of Johnston, using estrone in the growing girl, certainly do not encourage the view that small amounts of estrogens produce measurable nitrogen and calcium retention. Nor could Sherman, Gillett and Pope (30) demonstrate periodic fluctuations of nitrogen or phosphorus metabolism during 3 menstrual cycles in 2 normal women. Thorn and his coworkers (31) have suggested that the salt and water-retaining properties of the sex hormones are responsible for the conspicuous periodic gains in weight of some menstruating women Thorn and Emerson (24) however speak of special predisposing influences in such individuals. The entire matter of the general metabolic rôle of physiologic amounts of ovarian secretions in man therefore must be kept open, pending detailed quantitative study.[5]

The rôle of ovarian hormones in somatic growth is of especial importance in interpreting the mechanisms of the shortness of such girls as *A. B.* and *R. F.* who have manifest ovarian insufficiency and such high values of urinary gonadotropins as to indicate that their anterior pituitaries secrete as much gonadotropic material as those of the normal woman. Varney, Kenyon and Koch (13) and Albright, Smith and Fraser (32) have discussed this problem and called attention to the largely neglected series of German necropsies in which shortness of stature and ovarian aplasia were associated. Varney and his coworkers noted that the tallness of certain hypogonad women rendered Rossle's hypothesis (33) that the ovaries were essential for the attainment of normal stature difficult to accept, but pointed out that ovarian insufficiency might be of importance in cases where the growth endowment of other origin was imperfect. The present studies demonstrate that the tissues of these people may retain certain of the constituents of protoplasm, either under the influence of estradiol benzoate (*A. B.*) or testosterone propionate (*R. F.*). It should be noted that the rôle of feminine androgens as well as of estrogens must be considered in the study of the girl's growth. Wilkins, Fleischmann and Howard (20) observed growth of short poorly developed girls with methyl testosterone, although not with diethylstilbestrol.

In numerous experiments on the growing rat and mouse, estrogens in large amounts have been shown to have a dwarfing effect. Loss of nitrogen accompanies the diabetogenic action of estrogens in rats (34, 35). Nowhere in our work or in that of others, with the possible exception of that of Johnston, has any metabolic influence compatible with such properties been described in man. All human metabolic studies, however, have necessarily been brief and extreme dosages have been avoided. The cessation of feminine growth within a few years after menarche, at a time when high levels of estrogen secretion are sustained by the human ovary, suggests the need for search for properties of the estrogens more compatible with the growth inhibition observed in rodents.

SUMMARY

1. Five mg. of testosterone propionate intramuscularly daily in 2 eunuchoids produced characteristic reduction in urinary nitrogen, inorganic phosphorus, sulfate and sodium excretion. In one, urinary potassium was reduced. Creatinuria when sustained at high levels by creatine ingestion, was reduced by the androgen. Basal heat production was unaltered. The eunuchoid organism is thus quite sensitive to the metabolic effects of androgens.

2. Five mg. of estradiol benzoate, intramuscularly daily in 2 eunuchoids, one hypogonad woman and one normal woman induced reduction in urinary nitro-

[5] Dr. Ephraim Shorr has kindly permitted me to state that unpublished data of his demonstrate that estradiol benzoate in physiological doses as judged by vaginal smears will induce distinct nitrogen retention in amenorrheic girls and young women.

gen, inorganic phosphorus and sodium excretion. Urinary sulfate was probably reduced in one eunuchoid and in the women. Urinary potassium was elevated in the normal woman. Otherwise it was unaffected. Creatine excretion in the eunuchoid, when sustained at high levels by creatine ingestion, was not reduced by estradiol benzoate. This is in contrast to the effect of the androgen. Basal heat production was unaltered. Several of the metabolic effects of testosterone propionate are shared by estradiol benzoate given in sufficient amounts.

3. A masculinized girl (adreno-genital syndrome) showed none of the usual metabolic effects of estradiol benzoate. Creatinuria was increased.

4. Hypogonad women of short stature and with high urinary gonadotropin titers respond well to the metabolic influences of either estradiol benzoate or testosterone propionate.

5. It is not yet clear that the ovarian secretion in physiologic amounts exerts any general anabolic influence on non-genital tissue.

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Comparison of Metabolic Effects of Testosterone Propionate with Those of Chorionic Gonadotropin[1,2,3]

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IN A PREVIOUS communication we have noted that several of the metabolic effects of testosterone propionate in the adult eunuchoid could be observed in fairly well defined form with a dosage as low as 5 mg. daily (1, 2). This considerable sensitivity of the organism to the androgen is of great interest since such small amounts of testosterone propionate seem to fall well below requirements for replacement in adults, a s nearly as these can be judged by repair of secondary sex characteristics and maintenance of normal urinary androgens (discussed in ref. 1). Since many of these metabolic phenomena appear to be the chemical expressions of non-genital tissue growth (3, 4) it becomes likely that the androgens may play a part in somatic growth at a time when the evolution of secondary sex characters is at least not conspicuous. Normally the boy's pubertal growth spurt is apparent some time before the appearance of axillary hair (5). Well-defined growth in height and weight in boys has now been induced by several observers using testosterone propionate intramuscularly (6, 7, 8) and methyl testosterone orally (9, 10). Chorionic gonadotropin likewise produces an increase in height and weight of boys (11, 12), presumably by virtue of stimulation of the testes. These phenomena were predictable from early clinical studies of the victims of testicular tumors producing androgens (13, 14).

It is therefore quite reasonable that the metabolic effects of testosterone propionate or methyl testosterone and those of the testicular hormone should coincide. Nevertheless, the identity of the actual secretion of the testis cannot be said to be established, however probable testosterone seems to be as a candidate (15). It is accordingly of importance to compare the metabolic effects of the synthetic agents with those of the testicular hormone itself in some detail. Enhanced testicular secretion may be induced by chorionic material in suitably sensitive immature boys; such a 13-year-old boy, previously shown to be responsive, was utilized in this study. Chorionic material is not known to exert effects on somatic tissues of mammals other than those mediated through the gonads. It has not been possible for us to secure explicit control of this point however by the study of a youthful castrate. The view that any metabolic effects of chorionic material represent the consequences of testicular stimulation only thus remains an assumption, albeit a likely one. The current press of circumstances prevents inclusion of more subjects but the results obtained in the boy *R. D.* seem sufficiently decisive to record.

METHODS

The subject, *R. D.*, was studied in the hospital and given a constant diet. The chemical and metabolic methods used have been described previously (2, 4). Aliquots of urine for chemical study were set aside and the rest of the urine was extracted with benzene after hydrolysis for 15 minutes and then separated into neutral (androgenic) and phenolic (estrogenic) fractions (16). Androgens were determined by response of the chick comb, as described by Johnston and Koch (17); 17-ketosteroids were determined on the neutral fraction by Holtorff and Koch's modifica-

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[2] The urinary assays were made possible by a grant from the Committee for Research in Problems of Sex of the National Research Council, and by the Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

[3] The testosterone propionate (Oreton) and chorionic gonadotropin (Pranturon) were provided by Dr. Erwin Schwenk and Dr. Max Gilbert of the Schering Co., Bloomfield, N. J.

tion of the Callow technique (18); estrogens by the method of Varney and Koch using uterine weight in the immature mouse (19). Values for the androgens are expressed in international units (1 I.U. = activity of 0.1 mg. of androsterone); for the 17-ketosteroid in terms of color production equal to that of stated amounts of androsterone; and estrogens in equivalents of estrone (1 microgram equivalent = 10 I.U.)

PROTOCOL

R.D., an intelligent Italian boy, was first seen by us in 1937 when he was 9 years old. He had weighed 7 lb. 3 ounces at birth, following a difficult instrumental delivery. Growth had been slow since; at 9 he was 3 ft. 9.5 in. (117 cm.) tall and weighed 43 lb. (19.9 kg.). There was no family history of dwarfism. Except for bilateral undescended testes no further important defect was apparent on physical examination. His head seemed relatively large and the frontal bones were prominent. A roentgenogram of the sella turcica, repeated in 1941, showed nothing unusual. A series of films of the right hand is available. In 1937, at the age of 9, the epiphysis of the distal ulna, and the greater multangular had not appeared and the lesser multangular and scaphoid were very small. According to Todd's standard (20) his bone age was a little below 6 years. In 1938, at age 10, the ulnar epiphysis and the greater multangular had appeared and enlargement of all carpal bones was distinct. His status was about 7 years and 3 months according to Todd. In 1939, at 11, only the pisiform was absent. In 1941, at 13, all carpal bones were present and of good size, and the only evidence of departure from the standard lay in the relative lack of compact disposition of the carpal bones. Age is difficult to estimate at this time but a retardation of two years may have been present. A steady, if delayed, growth and maturation had proceeded through the years of observation. His growth in height of 21 cm. in 4.5 years, as compared to an average normal growth of about 25 cm., is in accord with this. Dentition departed somewhat from this picture, being well in advance of schedule, even at the age of 9. Dr. Blayney noted, for example, that the cusp of the lower left second molar could then be felt beneath the soft tissue indicating imminent eruption of a tooth not usually present before 12. The incisal halves of the central incisors were hypoplastic, indicating defective calcification at one period in his childhood. This defect was not apparent elsewhere.

Fundi and visual fields were not abnormal. Basal metabolic rates of +29 and +15 (Mayo Foundation standards) at 9 were not in accord with the clinical findings. Numerous subsequent determinations ranged from +2 to −9. A urea clearance at the age of 13 was 36 $\left(\frac{U}{B}\sqrt{V}\right)$, slightly below a normal range of 40 to 65. Blood urea N was 10.5 gm. per cent; serum inorganic phosphorus, 5.2 mg.%. The results of urine examination were repeatedly negative. The intravenous insulin tolerance test of Albright, Fraser and Smith (21) was normal in 1941. The serum Wassermann and Kahn reactions were negative, and red and white cell counts, differential and hemoglobin were normal.

On two occasions previous to the metabolic study recorded here courses of treatment with pregnancy urine extract were undertaken. The first course between July 19, 1937 and February, 1938, resulted in the emergence of the right testis into the inguinal canal and some growth of the phallus. Between March 2 and July 5, 1940, he received 1 grain of thyroid daily. A scant amount of pubic hair was first noted in April, 1940, at the age of 12, and 5 months later a rounded prostate, the area of a nickel, could be felt for the first time. The position of the testis however had not improved and since puberty was appearing spontaneously, it was necessary to proceed with surgery. A preliminary course of chorionic gonadotropin,[3] 150 I.U. 3 times weekly for 2 weeks and 750 I.U. 3 times weekly for 2 weeks, evoking further enlargement and hyperemia of the phallus, did not produce descent of the testes.

On Dec. 18, 1940, Dr. Vermeulen performed the first stage of a bilateral Torek orchidopexy. A large right testis 3 cm. long was found at the internal inguinal ring and a smaller left testis 1 cm. long was located above the internal ring. Fibrous bands investing the spermatic cords were severed and the left spermatic artery and vas deferens freed behind the peritoneum so that both testes could be brought into the scrotum, and anchored to the thighs. The second stage was performed in June, 1941. In the fall of 1941 both testes were in satisfactory position and of normal consistency, the right measured 4 × 3 × 3.4 cm., the left 3.6 × 3.0 × 2.2 cm. The phallus was 6 cm. long, the prostate about 2 cm. in diameter. A small amount of public and axillary hair was present. The voice was juvenile. In the year subsequent to the studies reported here the voice deepened decidedly and he grew 4 cm. in height without treatment.

It is not possible at present to account for the subject's short stature. His growth is now proceeding at a fairly normal rate. Some obscure factor operated in early childhood to retard progress temporarily. Malnutrition may have played a part, as his mother spoke of his poor appetite during his childhood. Urinary gonadotropins,[4] gave a value of 20 mouse units per 24 hours in the fall of 1940 when *R.D.* was 12. This normal figure was to be expected from the spontaneous growth of the patient's prostate gland at that time. Mechanical factors seemed to have impeded testicular descent.

In September, 1941, the boy, then 13, entered the hospital for metabolic study. He was at that time 138 cm. (4 ft. 6 in.) tall and weighed 35.3 kg. (78 lb.). Results of 6 basal metabolic rate determinations ranged from −8 to +2 (Mayo Foundation standards) averaging −5, yielding from 1185 to 1328 Calories per 24 hours, averaging 1238. He was placed on a constant diet of C 266 gm., P 66 gm., F 117 gm., Cal. 2381. This was estimated to contain N 10.6 gm., S 0.59 gm., P 1.28 gm., Ca 1.28 gm., K 3.65 gm. and Na 1.07 gm. To this 4 gm. of NaCl was added at the table. The fluids, including distilled drinking water, were kept constant in composition and amount

[4] The urinary gonadotropins were determined by R. F. Varney of the Department of Biochemistry.

(1850 cc. daily). He attended school regularly, taking his prepared lunch and carrying a bottle for one urination at home at noon. We are greatly indebted to both the boy and his mother for their patient coöperation. The values for the urinary creatinines were reasonably consistent and it is believed that there were no serious errors. There was insufficient time on school mornings for breakfast, basal metabolic rates and school so that we have insufficient data on heat production during the course of treatment. Scattered readings are listed according to the days in figure 1 and provide no evidence of significant change.

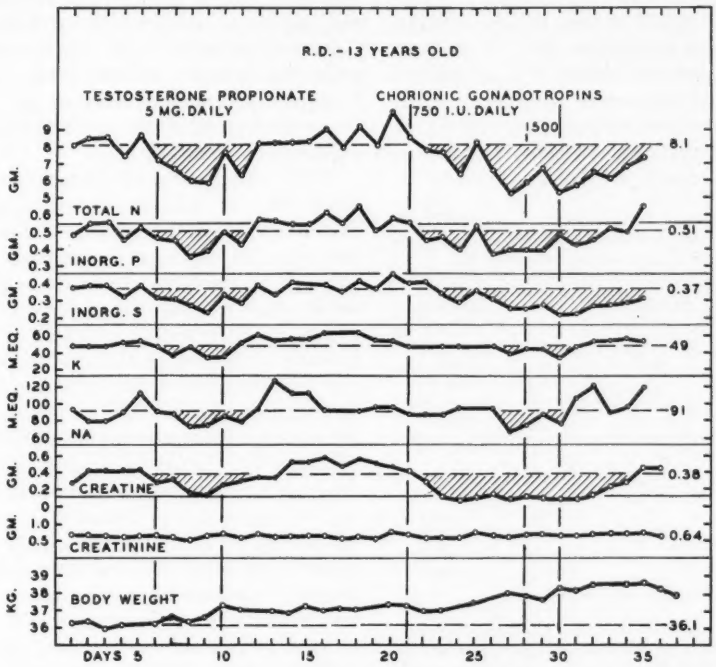

Fig. 1. Comparative metabolic effects of testosterone propionate and chorionic gonadotropin on *R. D.*, a short but growing boy in the early phases of spontaneous puberty.

Day	B.M.R.	Cal. per Hour	R.Q.
4	+2	55.4	0.80
11	−3	53.7	0.83
18	−7	51.5	0.86
25	±0	55.3	0.80
32	+2	57.2	0.80

DISCUSSION

R. D., a short but growing 13-year-old boy with a few signs of early puberty, responded in much the same manner to 5 mg. of testosterone propionate daily (fig. 1) as do adult eunuchoids to this amount (1, 2) or more (3, 4). The 45 mg. of nitrogen retained per kg. per day at the time of maximum effect of the androgen corresponds very closely to the 27 to 41 mg. recorded for the 3 eunuchoids receiving an identical dose; the depression of urinary inorganic phosphorus, sulfate, potassium and sodium is as great in the 13-year-old boy if allowance is made for the greater variability of these effects. Creatinuria was depressed by testosterone propionate as it was in several eunuchoids showing considerable amounts of creatine in the urine while on a general diet (3) or ingesting creatine (2, 4). This point is of interest in view of Duckworth's finding that the creatine tolerance of normal boys in the age range of 7 to 15 years could not be altered by testosterone propionate (22). *R. D.*'s weight increased at the usual time during treatment and to the usual extent but the baseline was not resumed on cessation of the injections, and the entire effect may be considered blurred by his tendency to gain weight throughout the experiment. As noted in the protocol, scattered readings indicated no modification of basal heat production or of the respiratory quotient.

Chorionic gonadotropin, 750–1500 I.U. per day, induced a general metabolic response in *R. D.*, the pattern of which corresponds very well to that observed with testosterone propionate. The more gradual return of the affected urinary constituents toward the baseline on cessation of treatment with the gonadotropin is not to be stressed. In numerous ex-

periments with testosterone propionate previously undertaken here (2, 3, 4) the resumption of baseline values has required more time than in *R. D.* It is not clear, however, that the effects of chorionic gonadotropin correspond precisely to those of methyl testosterone given orally. While methyl testosterone produces distinct reduction in urinary nitrogen, inorganic phosphorus, sodium, potassium and chloride (9, 10) Wilkins, Fleischmann and Howard (10) have clearly shown that it will, in time, increase creatinuria in the boy on a creatine-free diet. While much more detailed comparison between testosterone propionate and methyl testosterone is necessary in this regard, the present experiment suggests that the testicular secretion may differ from methyl testosterone in its influence on creatine metabolism.

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE AND CHORIONIC GONADOTROPIN ON URINARY STEROIDS OF *R. D.*

Day	No. days	Androgens, I.U./day	17-ks., mg./day	Estrogens, μg. estrone/day
Control	6	4–6	7.2	1
Control	12	6	6.2	<0.5
7–10	4	6	5.7	<1
11–16	6	6	4.8	1
17–20	4	7	5.4	1–2
22–27	6		7.6	0.5
28–30	3	5–6	6.6	<0.7
31–36	6		4.6	0.6
37–41	5		4.6	0.2

Five mg. of testosterone propionate was given daily from *day* 6 through *day* 10; 750 I.U. of chorionic gonadotropin was given daily from *day* 21 through *day* 27, 1500 I. U. of chorionic gonadotropin was given daily from *day* 28 through *day* 30. The numeration of days corresponds to that in figure 1.

The amount of nitrogen retained under the influence of chorionic gonadotropin at the time of maximum effect is 65. mg. per kg. per day. This is somewhat greater than was secured with 5 mg. of testosterone daily in *R. D.* or in the 3 eunuchoids studied. It corresponds very well with the 63 mg. per kg. per day average (range 51–83) for 6 experiments in 5 eunuchoids receiving 25 mg. of testosterone propionate daily. The individual variation in the degree of influence exerted by testosterone propionate on other urinary constituents is greater than with nitrogen. It is often difficult to relate the extent of effect to dose or to secure greater consistency by taking body weight into account. One may, however, say that the effects of chorionic gonadotropin are as substantial as those of 5 mg. or more of testosterone propionate daily. The rather insignificant reduction in urinary potassium with the chorionic material may be matched by the complete absence of effect of 5 mg. of testosterone propionate in the eunuchoid *J. X.* (2) A comparative table of the data on several subjects is given in another paper (23).

We regret that we are unable to present data on calcium metabolism. It is highly desirable that this be undertaken. The growth in height and development of bone described in children receiving several androgens and chorionic gonadotropin attests to the eventual deposit of calcium salts in these individuals. Calcium retention has been clearly shown to occur under the influence of testosterone propionate in Cushing's syndrome (24) and in an aged man with osteoporosis (25) and is to be expected in the child given sufficiently protracted study.

Table 1 shows that the urinary excretion of 17-ketosteroids, of androgens and of estrogens was unaltered during treatment with either testosterone propionate or chorionic gonadotropin. It has been abundantly demonstrated that the larger amounts of testosterone propionate will produce notable increases in urinary androgens (26–29). Fewer data are available concerning small doses. Holtorff and Koch (18), however, have recorded both colorimetric and biologic assays on the urine of our eunuchoid *J. K.* (1) while he was receiving 5 mg. of testosterone propionate daily. His control levels were 21. I.U. of androgenic activity and 6 mg. of 17-ketosteroids per day. During 15 days of treatment he averaged 43 I.U. and 8.5 mg. per day. This represents a 52 per cent recovery of the injected testosterone, if the urinary androgen be assumed to be androsterone and a 60 per cent recovery as a 17-ketosteroid. The values for recovered biologic activity are somewhat, but hardly seriously, above those found when 20 to 25 mg. of testosterone propionate are given daily to hypogonad men, if the same assumptions are made in the calculation (27, 28). On any such basis *R. D.*'s biologic assay should have risen 22 I.U. per day and his 17-ketosteroids 2.5 mg. per day. While the latter increase may have been obscured by fluctuations in the day-to-day excretion it seems likely that any such increase in biologic assay would have been detected in view of the constancy of the low androgen values recorded throughout the experiment. We have no explanation at this time for this result. The recovery values in *J. K.* may well be exceptionally high and serve poorly as a guide. In any event, it is of interest that the metabolic effects of both testosterone propionate and chorionic gonadotropin were distinct at times when urinary assays gave no hint of heightened activity of testis hormones in the body. It is likely, therefore, that the testis may make substantial contributions to the growth process in the child, without inducing any measurable urinary representation of such contributions. The appearance of increased

amounts of such a derived steroid as androsterone is not a necessary companion of physiologic response.

SUMMARY

In a 13-year-old boy 5 mg. of testosterone propionate daily induced reduction in urinary excretion of nitrogen, inorganic phosphorus, sulfate, potassium, sodium and creatine.

Chorionic gonadotropin (750 to 1500 I.U.) exerted essentially the same effects as testosterone propionate. In several respects the influence was more powerful than that of 5 mg. of testosterone propionate daily.

The metabolic influences of both agents were unaccompanied by any change in the urinary excretion of androgens, estrogens or 17-ketosteroids.

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Metabolic Response of Aged Men to Testosterone Propionate[1,2]

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IN 1889 BROWN-SEQUARD (1), then 72 years old, injected a testicular extract into himself and experienced a return of his youthful sense of well-being. Since this historically important, though unreliable experiment, Brown-Sequard's guiding idea that the testis might play some decisive rôle in somatic senescence has never been entirely lost sight of, even though it has acquired little substantial support. Such a rôle demands that the testicular hormone exert some important metabolic effect upon non-genital tissues, that hormone secretion be reduced during the declining years and that aged tissue retain sufficient sensitivity to the hormone to make any deficit in secretion one of material consequence.

It is now apparent that testosterone propionate, when given intramuscularly to the hypogonad or normal man or woman, exerts metabolic influences which are compatible with the formation of new non-genital tissue (2–5). Methyl testosterone given orally evokes much the same response, although some differences in detail may exist (6). Although there are many uncertainties concerning the site of this new tissue deposit, and the functional consequences of such effects remain a matter for speculation, we must now regard the testis as exerting a complex anabolic influence in human economy. Thus the Brown-Sequard hypothesis, often seeming the oldest of endocrinological foibles, requires re-examination.

The age of tissue often materially influences the response to hormones. Engle (7) has reviewed this problem with respect to testicular function. Thus, the seminiferous epithelium of the testis of the growing rat responds to gonadotropins with sperm formation only when the animal is old enough (7). Hooker (8) has described a special enhancement of sensitivity of the seminal vesicles of the castrated rat to androgens at the time of normal puberty. The focal regression of prostatic epithelium of man, beginning in the forties (9) is compatible with diminished androgen production by the testis, but Moore and McLellan (10), unable to detect modification of such tissue by pre-operative administration of testosterone propionate, suggest loss of local sensitivity to the hormone as a decisive factor in senile prostatic atrophy. Carcinomatous prostatic tissue, however, often retains some dependence upon testicular androgens and may regress after castration according to the brilliant and provocative work of Huggins and his associates (11, 12). Since the sensitivity of aged tissue to androgens must be known in order to evaluate the usefulness of any testis hormone available, and to estimate the consequences of any deficit, we have extended our studies on the metabolic effects of testosterone propionate to two old men. Such work is a useful preliminary to the more difficult task of interpreting these chemical effects in terms of the well being of the individual.

METHODS

The subjects were placed in the hospital and given a constant diet providing sufficient caloric intake to maintain an approximately constant weight and to permit moderate activity about the wards. Metabolic and chemical methods used have been previously described (3, 5) with the exception of that for capillary blood-glucose on *M. L.*, which was determined by the method of Miller and Van Slyke (13).

Through the courtesy of our colleagues in the Department of Biochemistry working under Dr. F. C. Koch we are able to quote assays on the urine of these subjects. The 17-ketosteroids were measured as described by Holtorff and Koch (14); androgens, by the capon's comb, using an inunction prodecure soon to be described by Johnston and Koch; estrogens, by induction of estrus in the spayed rat, the details of

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[2] The testosterone propionate used was generously provided by Dr. Erwin Schwenk and Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J.

which are given by Koch (15). Extraction of these steroids was conducted as previously described (16). Gonadotropins in the urine were precipitated by alcohol and assayed by increase in weight of the uterus of the immature mouse (17).

Through the courtesy of our colleague in the Department of Surgery, Dr. W. W. Scott, we are able to quote his determinations of the urinary acid phosphatase on our two aged men. The method used, together with norms at various ages, are given by Scott and Huggins (18). Determinations were made on fresh morning urine.

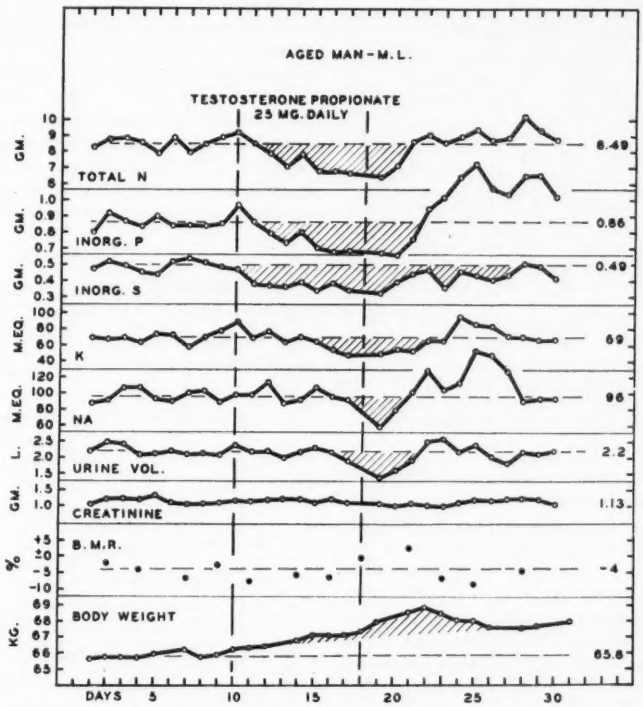

Fig. 1. Effect of intramuscular injections of testosterone propionate on several urinary constituents, basal metabolic rate and body weight of the 76-year-old man *M. L.*; 25 mg. was given daily from *day 10* through *day 18*. Sulphate expressed as S was determined.

PROTOCOLS

M.L. was a 76-year-old man, a patient of Dr. H. T. Ricketts who kindly permitted us to make these observations. Save for a moderate grade of arteriosclerosis, a moderate enlargement of the prostate gland which had provoked no disturbance in the function of the urinary tract and a slight hypertension (150/172/76–90 mm. Hg) there were no abnormalities on physical examination. The urea clearance was somewhat reduced giving a value of $44\left(\frac{UV}{B}\right)$ as compared to a normal range of 60 to 90. Traces of glucose were commonly found in the urine. Blood-glucose values in mg. per cent during a glucose tolerance test follow: fasting, 88; ½ hour, 194; 2 hours, 211; 3 hours, 174. From + to ++ reduction appeared in the urine in all samples after the fasting specimen. This was interpreted as demonstrating a mild diabetes mellitus.

A 6-day-urine collection showed the presence of 11.3 mg. of 17-ketosteroids (colorimetric) and the equivalent of 8 to 9 microgram equivalents of estrone per day. These may be taken as normal. Urinary gonadotropins were 20 to 30 and 50 mouse units per day which likewise may be regarded as normal, the latter value however being a little high.

He was studied in January, 1941. At this time the diet comprised C 200, P 72, F 161, Calories 2537. This was estimated to provide 11.5 gm. of N, 0.87 gm. of S, 1.67 gm. of P, 1.71 gm. of Ca, 3.85 gm. of K, 1.27 gm. of Cl. To this was added 4 gm. of NaCl at the table. The fluid intake, including distilled drinking water, was maintained at 2900 cc. daily. The basal metabolic rate, after training, averaged −4 (Mayo Foundation standards) yielding 1439 Calories per 24 hours. By virtue of a diet somewhat high in calories he gained a little over 2 kg. during the month of the experiment, a gain not attributable to the treatment with testosterone propionate. As seen in table

1 little or no hyperglycemia occurred on this regime. Urinary reducing substances were usually absent or present only in traces.

The details of the metabolic influence of testosterone propionate are shown in figure 1 and table. 1. Urinary calcium, which is not so recorded, was uninfluenced by treatment. A 4-day control period (*days* 6–9) showed 0.064 gm. per day, a 3-day period (*days* 15–17) showed 0.075 gm. per day, and a 3-day recovery period (*days* 29–31) showed 0.069 gm. per day. The androgen had no

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE ON VARIOUS BLOOD CONSTITUENTS OF THE AGED MAN, *M. L.*

Day	Blood Urea N mg. %	Serum P (inorg.) mg.%	Glucose in Blood[2] mg.% at Hours			
			7:30	11:15	4:15	9:15
1	12.7	3.5	109	101	113	110
3	13.1	3.4	113	102	108	116
8	9.8	3.3				
10[1]	11.0	3.6	102	113	104	125
15	8.2	3.5	97	101	113	111
17	7.8	2.7	103	103	131	122
22	10.8	3.6	109	119	118	
24	11.2	3.9	103	97	115	120

[1] Testosterone propionate 25 mg. daily intramuscularly was given from *days* 10 to 18 inclusive.
[2] Blood glucose was determined on capillary blood.

effect either on *M.L.*'s sexual excitability or on his sense of well being. As in our previous work there was no influence on pulse rate, blood pressure or fasting respiratory quotient. These values are, accordingly, not given. Ten control determinations for urinary acid phosphatase averaged 10 units per 100 cc. (range 1.8–20.5). Five determinations during treatment averaged 10 units (range 3.4–25 units). These values are well below those of normal young men, who average about 60 units per 100 cc. (18).

S.F. was a 76-year-old man with a blepharospasm, due in all probability to arteriosclerotic degeneration of the extra-pyramidal brain centers. His physician, Dr. R. B. Richter, kindly permitted these studies. Except for this defect and for an enlarged prostate and lenticular opacities, there was little abnormal on physical examination. The urea clearance was somewhat reduced, giving values of 24 and 23 $\left(\frac{U}{B}\sqrt{v}\right)$ as compared to a normal of 40 to 65. There was no abnormality of the urine by routine tests. The patient's blood Wassermann reaction was repeatedly strongly positive, the Kahn reaction negative. In view of his age this matter was not pursued further and the syphilis was regarded as latent. A 5-day-urine collection yielded 14 mg. of 17-ketosteroids (colorimetric) per day, 56 I.U. of androgenic activity, and less than 5.5 microgram equivalents of estrone. Urinary gonadotropins were 30 to 40 mouse units per day. These are all normal values.

He was studied in February and March of 1941. The diet comprised C 285, P 58, F 87, Calories 2155, and was estimated to yield 9.3 gm. of N, 0.80 gm. of S, 0.98 gm. of P, 3.4 gm. of K, 1.03 gm. of Na. To this was added 4 gm. of NaCl at the table. The fluid intake, including distilled drinking water, was kept at 2300 cc. daily. The basal metabolic rate, after training, averaged −5 (Mayo foundation standards) giving 1267 Calories per day. Since from 50 to 100 cc. of residual urine remained after urination, each collection period was begun and terminated by catheterization and the urine for each period was pooled for analysis.

The details of the metabolic influence of testosterone propionate are given in figure 2. Values for blood urea nitrogen and serum inorganic phosphorus were normal and unaltered by treatment, and so are not recorded. As in *M.L.* the androgen had no influence on sexual excitability or sense of well being. Eight determinations of urinary acid phosphatase before treatment averaged 33 units per 100 cc. with a range of 26 to 41. Seven determinations during treatment averaged 38 units with a range of 27 to 49.

DISCUSSION

The data given in figures 1 and 2 and in table 1 on the two 76-year-old men, each receiving 25 mg. of testosterone propionate daily, discloses no sharp variation in pattern from that previously recorded

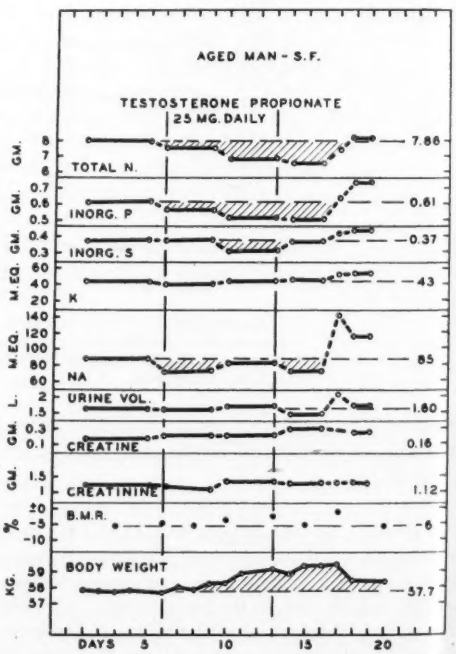

Fig. 2. EFFECT OF INTRAMUSCULAR INJECTIONS OF TESTOSTERONE PROPIONATE on several urinary constituents, basal metabolic rate and body weight of the 76-year-old man *S. F.*; 25 mg. was given daily from *day* 6 through *day* 13. Sulfate expressed as *S* was determined.

for hypogonad men (2, 3, 5) and women (5) and normal men and women (3). The decline in urinary nitrogen and inorganic phosphorus begins promptly and is well sustained. As is often the case in our other subjects the more complete data on *M. L.* shows no evidence of a conspicuous compensatory loss of nitrogen through the urine after cessation of injections, thus indicating that aged tissue may retain nitrogenous material as tenaciously as more youthful tissue. The not reduced by testosterone propionate. Even in the eunuchoid, creatinuria of this grade occurring when the patient is on a general diet, may be little influenced by the antrogen (3, fig. 2). The rise in basal heat production expressed either as basal metabolic rate or as total Calories per hour, is only suggestive in *M. L.* and *S. F.* under the influence of testosterone propionate. In the eunuchoid the increase in heat production may seem more distinct in the first 10 days

TABLE 2. MAXIMAL REDUCTION INDUCED BY ANDROGENS IN URINARY EXCRETION OF SUBSTANCES

Subject[1]	Condition	Age, yr.	Weight kg.	Testosterone Propionate, daily mg.	N gm./day	N Retention gm./kg./day	P gm./day	P Retention mg./kg./day	S gm./day	K m.eq./day	Na m.eq./day	Cl m.eq./day
J. K. (4)	Eunuchoid	26	77	5	3.04	0.039						
J. X. (5)	Eunuchoid	29	66	5	1.80	0.027	0.10	1.5	0.06	0	21	
J. D. (5)	Eunuchoid	34	76	5	3.13	0.041	0.31	4.1	0.18	17	29	
Average				5	2.66	0.031						
J. K. (4)	Eunuchoid	26	77	10	4.62	0.060						
J. K. (4)	Eunuchoid	26	77	25	6.40	0.083						
F. R. (2)	Eunuchoid	27	74	25	5.14	0.070					25	22
J. X. (3)	Eunuchoid	27	62	25	3.27	0.053	0.24	3.9				
N. D. (2)	Eunuchoid	31	53	25	3.03	0.058					23	0
N. D. (5)	Eunuchoid	33	60	25	3.08	0.051	0.21	3.5				
M. D. (2)	Eunuchoid	51	50	25	3.19	0.064					30	10
Average				25	4.02	0.063						
J. K. (4)	Eunuchoid	26	77	50	6.23	0.081						
J. X. (3)	Eunuchoid	27	61	50	2.93	0.048	0.29	4.8		25	26	29
Average				50	4.58	0.061						
J. X.	Eunuchoid	29	65	100[2]	3.23	0.050						
H. S. (2)	Eunuchoid, hypopituitary	24	64.6	25 test. prop.	1.59	0.025				13	31	20
R. D.	Short boy	12	36	5 cho. gonadotr.	1.61 2.34	0.045 0.065	0.08 0.09	2.2 2.5	0.09 0.13	13 9	17 18	
J. L. (3)	Normal man	19	86	25	2.55	0.030	0.16	1.9		17	45	46
R. W. (3)	Normal man	21	56	25	1.66	0.029	0.29	5.5		12	20	18
M. L.	Aged man	76	59	25	1.79	0.027	0.19	3.2	0.14	17	42	
S. F.	Aged man	76	58	25	1.32	0.023	0.11	1.9	0.07	0	13	
R. F. (5)	Hypogonad woman	24	45	25	2.52	0.056	0.24	5.3	0.21	14	43	
P. J. (3)	Normal woman	24	61	25	2.61	0.043	0.28	4.6		10	15	19
E. S. (3)	Normal woman	31	45.6	25	0.73	0.016	0.12	2.6		12	22	18

[1] The original data summarized here are given in the references indicated by the figures in parentheses after the patient's initials. The body weight used in the calculations is the average pre-treatment weight.
[2] 100 mg. methyl testosterone.
[2] Chorionic gonadotropin in addition to testosterone propionate.

phosphate diuresis is, on the other hand, more striking than usual in *M. L.* This may, however, constitute a merely individual peculiarity. Values for urinary inorganic sulfate decline with those for nitrogen and inorganic phosphorus, although the parallelism is not always perfect (*S. F.*, fig. 2). Urinary potassium is reduced in characteristic fashion in *M. L.* and is unaffected in *S. F.* Urinary sodium is reduced in both, although at different times, and exhibits the usual sharp post-treatment diuresis in both men. The reduction in urinary volume is well seen in *M. L.* but not in *S. F.* Both men show the weight gain previously described in normal and hypogonad men and women. The slight creatinuria of *S. F.* (200 mg. per day) was of treatment, but longer periods are often required to demonstrate clearly the calorigenic properties of testosterone propionate (4). No elevation of the concentration of urea nitrogen in the whole blood or inorganic phosphorus in the serum was induced (table 1).

No alteration in the urinary calcium of *M. L.* (protocols) was produced by the androgen. Similarly in the eunuchoid *N. D.* (5) neither fecal nor urinary calcium was influenced by testosterone propionate during brief treatment periods. This, however, must not be taken to mean that androgens never influence calcium metabolism in aged men. In a man with senile osteoporosis, Reifenstein and his associates (19) in-

duced conspicuous retention of calcium as well as nitrogen and phosphorus with testosterone propionate. Whether calcium retention is determined by pre-existing atrophy of bone, or whether it can be observed in aged or other men with normal bones, who are given sufficiently protracted treatment, remains unsettled.

It is of interest that the blood glucose of *M. L.* was not altered by testosterone propionate (table 1) nor was the slight irregular glycosuria increased. No indication was apparent of the diabetogenic properties of testosterone propionate described by Ingle (20) with massive doses in the partially depancreatized rat on a high carbohydrate diet or by Dolin, Joseph and Gaunt (21) in the partially depancreatized ferret.

The intensity of response of the aged men compared with that of others may be best seen by examining table 2. The variable length of the several experiments can best be taken into account by attention to the maximal effect of the androgen. As pointed out first by Kochakian and Murlin (27) in the castrated dog, any given dose of the androgen exerts its maximal influence on urinary nitrogen excretion within a week to 10 days. Continuation of such dosage, within the limits of experiments thus far undertaken, does not further modify the response. Our experience in man indicates that this rule holds also for urinary inorganic phosphorus, sulfate and potassium excretion. It is not to be supposed that it would obtain indefinitely. Some obscure physiologic mechanism probably eventually terminates retention of these substances. Such limits, however, have never been well defined in our work which has involved treatment periods for as long as 2 months in the eunuchoid (nitrogen only) (4). Thus the maximal effect recorded in table 2 may be regarded as a fairly stable state and suitable for comparison of various individuals. Sodium and chloride excretion in the urine are, on the other hand, so irregular that the maximal effect of the androgen is not well sustained and the recorded figures represent points rather than plateaux.

The amount of nitrogen estimated as retained per kg. per day by our eunuchoids receiving 25 mg. of testosterone propionate per day ranged from 51 to 83 mg. and averaged 63 mg. That for the two normal young men amounted to 29 and 30, respectively. That for the two aged men reached values of 23 and 27 mg. per kg. per day, approximating the retention by the normal young men. Unfortunately no data are available on aged hypogonad individuals, although *M. D.*, a 51-year-old eunuchoid, retained as much nitrogen per kg. as younger eunuchoids. There seems to be no pressing reason for believing that our aged men suffered from gross testicular insufficiency, and hence should be compared with the eunuchoids. Physical examination did not suggest hypogonadism. *M. L.* had spoken of waning sexual interest but his wife had died not long before; *S. F.* led an active sexual life. The urinary 17-ketosteroids (11.3 and 14 mg.) and the androgens of *S. F.* (56 I.U.) were within the normal range for young men, although such determinations cannot be taken to measure testicular function only. Values for urinary gonadotropins were not abnormally high. The urinary acid phosphatase of *S. F.* was somewhat below average youthful levels and that of *M. L.* distinctly below. This reduction in prostatic function however may have been as much a matter of reduced sensitiveness to androgens as of diminished hormone production. Thus, although our aged men retained somewhat less nitrogen per kg. per day than our eunuchoids, there is not sufficient reason for believing that this difference was solely due to age. The effects of testosterone propionate on the other urinary constituents cited in table 2 similarly seem as striking in our aged men as in other subjects if due allowance is made for the considerable individual variability in response.

It is of interest that the metabolic effects of testosterone propionate in the aged men were distinct at a time when no effect upon the prostatic secretion of acid phosphatase was apparent (see protocols).

The functional significance of the anabolic effects of testosterone propionate in the aged, like that in others, remains to be determined. On the basis of exceptional muscle hypertrophy in the boy with precocious puberty due to interstitial cell tumors (23), of muscular growth in the guinea pig receiving testosterone propionate (24) and of the impression of growth of muscles given by eunuchoids receiving androgens, it seems likely that muscles may be a site of new tissue deposit. Their strength and efficiency may be improved, thereby, but more objective evidence of such improvement is needed. Since data from animal experiments indicate that androgens may induce growth of the liver (25) and kidney (25, 26, 27) these organs may likewise serve as sources of new tissue deposit and modifications of their function must be sought. Reifenstein and his coworkers (19) see an opportunity to repair atrophic senile bone by the use of testosterone propionate.

The processes of senescence do not seriously impair the capacity of the organism to respond to the metabolic influences of androgens. Such testicular hormones as are secreted may be held effective in this regard. The precise measurement of testicular hormone production is difficult and awaits more precise methods than have been thus far employed. There is accordingly considerable doubt as to the frequency of reduced hormone production by the aged testis (7). Such testicular insufficiency as exists may be ex-

pected to have metabolic consequences which play some part in the physiology of the aged.

SUMMARY AND CONCLUSIONS

1. Testosterone propionate, 25 mg. daily intramuscularly, reduced the urinary excretion of nitrogen, inorganic phosphorus, sulfate and sodium in two 76-year-old men and caused an increase in body weight. Urinary potassium was decreased in one subject. Basal heat production was increased slightly, if at all. The pattern of response was much the same as in younger individuals.

2. The amount of nitrogen retained (25 mg. per kg. per day at the time of maximal effect) equaled that retained by normal young men, and was less than that retained by younger eunuchoids. Other urinary constituents were affected as much in the aged as in younger subjects, if due allowance is made for individual variations.

3. Senescence, accordingly, does not distinctly modify the metabolic response to androgens. Such testicular insufficiency as exists in the aged may be conceived as having metabolic consequences the functional importance of which remains to be determined.

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Creatinin Excretion in Women: Clinical Significance in Obesity

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The daily excretion of creatinin on a meat-free diet is constant for each individual and is uninfluenced by many external factors (1, 2). Since creatinin originates from endogenous sources, the determination of its excretion values has been advocated as a measure of the active protoplasmic mass in the body. Shaffer believed it to be derived from some special process of normal metabolism taking place largely, if not entirely, in the muscles (3). Recent studies which confirm this view show muscle creatin as the source (4–7), the total being related to the 24-hour urine creatinin output (8, 9). Creatinin excretion, therefore, affords an index of the protoplasmic activity of the muscles and, indirectly, of the total muscle mass assuming this activity to be basal and constant. Folin first observed diminished excretion of creatinin at a given weight in the obese individual, suggesting the validity of the creatinin coefficient (3) as an index of nutrition.

In office practice, the optimal weight estimation of Willoughby (10), based on a number of bone measurements, has proven to be clinically simple and sound (11). As gauged by clinical impressions of results, the accuracy of the method diminishes with increasing weight, erring on the side of a too-severe optimal in the very obese type.[1] Since muscle mass could be expected to follow true skeletal proportions, an examination of the relationship between creatinin excretion and the Willoughby optimal weight appeared to be of interest. The value of a true optimal weight in the calculation of the basal metabolism of children has been demonstrated by the Talbot (12, 13, 14). The formulation of an optimal weight standard based on physiological evidences of muscularity (defined as creatinin optimal weight) assumed added importance in the belief that it would serve better than actual weight in the calculation of basal metabolism of obese individuals, in spite of the existing discrepancies between the relationship of total metabolism to creatinin excretion (15, 16, 17).

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[1] Willoughby points out that the cosmetic optimal may not coincide with the calculated figure because of a frequently disproportionate weight loss in the various parts of the body in the obese person.

Material and Method

This study is based on observations in 50 normal women between the ages of 20 and 45 years. Cases of diabetes as well as of thyroid and metabolic diseases other than obesity, *per se* were excluded. Careful clinical study eliminated those with infections, myopathies and diseases of the cardio-renal system. The basal metabolic rate, serum cholesterol, serologic, hematologic and urine examinations were performed in all cases. Urine collections were made at home under strict regulations of diet and activity for 3 successive days. Meat and meat products were prohibited, although milk, cheese and eggs were permitted. Total fluid intake was regulated to no more than 2 quarts daily. The patients were instructed to rest at home and avoid exposure to sunlight. Presence of fever, upper respiratory infection or active allergy disqualified results. Receptacles with preservative were provided and the patient was requested to bring to the office the complete and separate 24-hour urine specimens obtained during the last 2 days of the test. Good coöperation on the part of the patients and the adequate volume of the urine agreed with the consistency of results of the two successive days. Variations greater than ± 10 per cent were infrequent. Preformed creatinin was determined by the method of Folin (18) on 1 cc. of urine. An average of the 2 successive figures was taken and expressed to the nearest 50 mg.

Results and Discussion

The results of creatinin determinations in 50 patients are tabulated in table 1 and expressions for the relationship of creatinin excretion to weight in the normally proportioned (fig. 2) and in the obese woman (fig. 1) were derived. The optimal weights, as calculated by the method of Willoughby, were further correlated with actual values of the creatinin excreted for all of the 50 women (fig. 3). The relationship of these 3 linear equations to each other is demonstrated in figure 4 and a formula for the conversion of the optimal weight from the Willoughby standard to that of the creatinin optimal is presented in figure 5. Twenty-four-hour creatinin excretion

TABLE 1. CREATININ EXCRETION IN 50 ADULT WOMEN. RELATION TO ACTUAL WEIGHT, WILLOUGHBY-WEIGHT ESTIMATION AND CLINICAL IMPRESSION

Wt. Range, lb.	Case No.	Creatinin, mg. per 24 hr.	Actual Weight, lb.	Willoughby Weight Estimation, lb.	Height, in.	Bone Diameter	Weight Impression
	1	700	94	110	61	Small	Underweight
	2	800	108	110	59	Average	Plump
	3	800	112	100	63	Small	Plump
	4	850	108	110	62	Average	Normal
	5	900	102	110	64	Average	Underweight
	6	1000	110	120	68	Broad	Normal
	7	1000	109	100	64	Broad	Normal
	8	1000	115	115	62	Average	Normal
100–120	9	1000	107	110	64	Small	Normal
	10	1000	100	115	66	Average	Underweight
	11	1000	113	110	61	Average	Plump
	12	1050	116	115	64	Average	Normal, hirsute
	13	1050	105	110	65	Average	Normal
	14	1100	106	110	66	Average	Normal
	15	1100	110	100	61	Small	Plump
	16	1150	115	115	64	Average	Normal
	17	1150	118	120	66	Average	Normal, hirsute
	18	1250	100	110	61	Broad	Underweight, hirsute
	19	850	136	130	65	Small	Plump
	20	850	135	120	64	Small	Plump
	21	950	130	110	62	Average	Plump
	22	1000	115	115	65	Average	Normal, hirsute
	23	1100	122	125	64	Average	Normal
120–140	24	1100	116	115	60	Small	Normal
	25	1100	124	120	65	Average	Normal
	26	1150	132	125	64	Broad	Plump
	27	1150	123	130	68	Small	Normal
	28	1150	134	130	66	Average	Normal
	29	1200	123	120	66	Average	Normal
	30	1300	132	125	66	Average	Normal
	31	1100	164	120	62	Small	Obese
	32	1100	160	125	62	Small	Obese
	33	1200	148	106	62	Broad	Obese
	34	1250	148	140	66	Broad	Normal
140–160	35	1250	143	125	66	Small	Obese
	36	1350	154	120	63	Average	Obese, hirsute
	37	1350	143	125	65	Average	Obese, hirsute
	38	1400	149	130	63	Broad	Obese
	39	1850	152	140	68	Broad	Obese, hirsute
	40	900	162	130	63	Small	Obese
	41	1000	177	120	64	Small	Obese
160–180	42	1050	163	140	63	Broad	Obese
	43	1400	172	146	69	Broad	Plump
	44	1450	162	135	67	Broad	Obese, hirsute
180–200	45	1100	184	125	64	Small	Obese
	46	1150	203	150	63	Small	Obese
200–220	47	1400	200	145	61	Small	Obese
	48	1450	214	140	62	Broad	Obese, hirsute
220–plus	49	1700	245	140	65	Broad	Obese
	50	1550	279	142	66	Broad	Obese

values in the well-proportioned individuals form the standard for determination of the creatinin-optimal weight. The relation of the optimal weights, based on the Willoughby bone measurements, to creatinin excretion is not identical with the above. The lines cross each other at 123 pounds, the Willoughby figures presenting a smaller range, being too liberal at the lower weight figures and too severe at the higher. Practical experience with results in induced weight loss justified an arbitrary addition of 10 to 20 pounds to the Willoughby figure for best cosmetic results; this approximates the creatinin optimal standard. The above two equations are valid for more than 80 per cent of the cases if a variation of 150 mg. of creatinin at a given weight is admitted.

Weight for weight, the obese individuals excreted

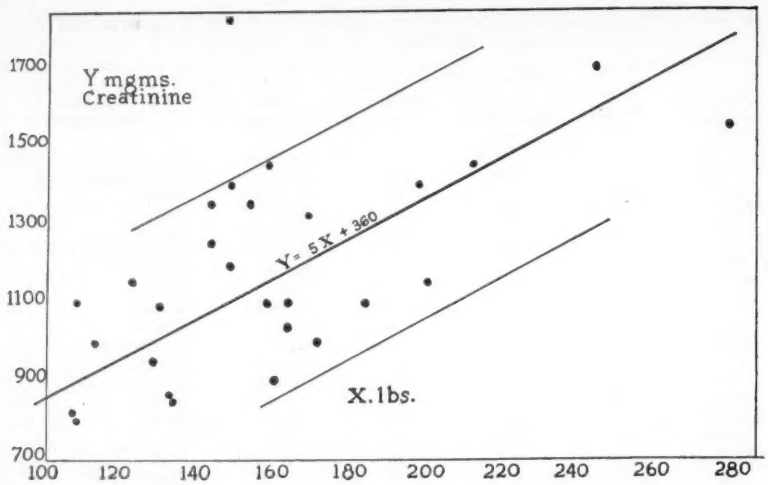

Fig. 1. Relationship of creatinin excretion (Y) to weight (X) in obese women. Variations of ±280 mg. true for 96 per cent of all values.

considerably less creatinin than the well-proportioned ones. Formulation of a linear expression (relationship of actual weight to creatinin excretion) in the obese women can be made with less certainty because of the striking variations in creatinin excretion from one individual to another at a given weight. When the same variation (+150 mg. of creatinin at a given weight) is admitted for this group as for those previously studied, the formula included only 42 per cent of the obese cases, thus disqualifying the observation. A variation of about ± 280 mg. must be admitted to permit a formulation here at all. A characteristic feature of obesity, therefore, is not only the lowered creatinin excretion in most of the cases, but also the great variability from one individual to another, depending on clinical evidence of muscularity. It may be added that the presence of hirsutism appears to influence creatinin excretion, *i.e.*, there is a greater output of creatinin probably because the hirsute individuals frequently are more muscular. Generally speaking, the degree of muscularity of the individual can be correlated with the levels of creatinin excretion (20, 21, 22). The finding of diminished creatinin excretion in the obese group, as a whole, supports this observation because, weight for weight, the obese individuals are less muscular. Conversely, there are a good many obese women who are more muscular than is apparent. Since the degree of muscularity is not always easily ascertained in the heavy female, creatinin excretion may be used as a valuable index thereof. The wide variations in creatinin excretion levels from one individual to another is to be emphasized, because it indicates that wide variations of muscularity or its physiological activity do exist. The total resting metabolism of the obese individual is known to be elevated (23, 24). The metabolic activity due to fat accounts for a small fraction of this increment, the remainder being due to the metabolic activity of the protoplasmic mass of other tissue (25). Thus, the presence of excess body fat requires in-

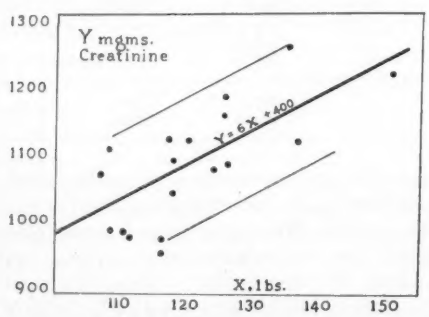

Fig. 2. Relationship of weight (X), to creatinin excretion (Y) in normally-proportioned adult women. Variations of ± 100 mg. true for 95 per cent of all values.

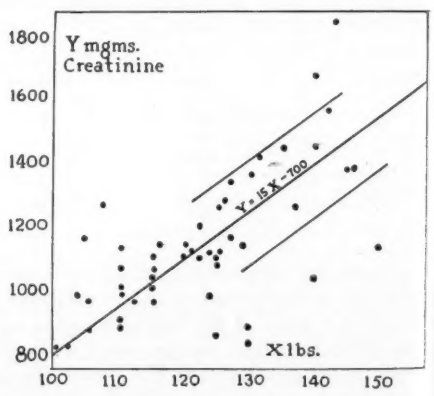

Fig. 3. Relationship between Willoughby optimal weight estimation (X) and creatinin excretion per 24 hours (Y) in 50 women. Variation of ± 150 mg. true for 82 per cent of all values.

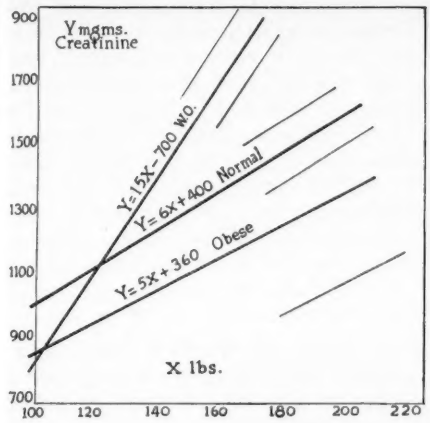

Fig. 4. Relationship of creatinin excretion per 24 hours (Y) and weight (X) in the obese and normal female. Estimations of relationship to Willoughby optimal (WO) weight.

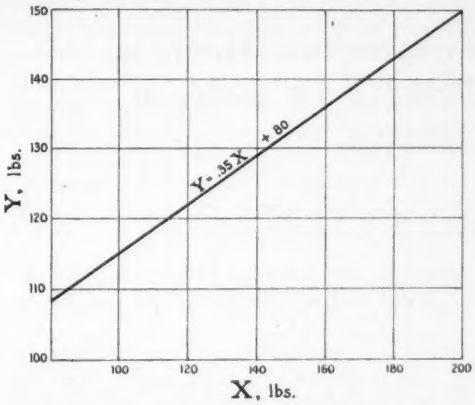

Fig. 5. Estimation of optimal weight. Relation between Willoughby optimal weight (Y) and optimal weight (X) based on creatinin excretion.

creased energy production on the part of the active tissues of the body. It may be recalled that 20 per cent of the obese individuals show variations in basal metabolism outside of the normal range which generally are not to be explained on the basis of thyroid disease. The question may be raised whether the discrepancies are due to variations in muscle mass or its activity, as demonstrated by creatinin excretion. The observation may be made that cases of so-called simple obesity do not form a homogeneous group. Obesity may be part of general bigness; when obesity is associated with large bones and muscle mass, the term macrosomic may be applied. Conversely, the small-boned and poorly muscled person may be termed a microsomic obese individual. Further examination of metabolic data in the light of these observations, *i.e.*, muscle mass and creatinin excretion, is indicated.

SUMMARY AND CONCLUSIONS

1. Linear equations expressing the relationship between body weight and creatinin excretion are derived on the basis of a study of 50 adult women.

2. For a known level of creatinin excretion in a given case (whether obese or not) an optimal weight of the patient may be determined by the application of the equation for creatinin-weight relationship established for well-proportioned women. This optimal weight is defined as creatinin-optimal weight.

3. In the absence of an actual laboratory determination, the creatinin excretion and creatinin-optimal weight may be calculated through a conversion equation from the Willoughby optimal weight estimation, based on bone measurements.

4. Creatinin-optimal weight is closely compatible with clinical weight evaluations and offers a physiologic basis for the quantitative expression of the nutritional state of the adult females.

5. Obese women generally excrete less creatinin than the well-proportioned ones and show more striking variations in the excretion levels from one individual to another at a given weight. These variations are generally in direct agreement with clinical impressions concerning the muscularity of the obese.

6. The desirability of clinically differentiating overweight individuals on the basis of muscle mass into the macrosomic and microsomic types is suggested to facilitate further metabolic studies in obesity.

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Premenstrual Headache Relieved by Estrogen Therapy[1]

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IN THE COURSE of a study of the sex cycle of the human female which is being made in this laboratory, a number of patients have been referred for various disturbances related to menstruation. Of these, one group of 6 patients present a rather constant syndrome, of which the chief complaint is premenstrual headache and a report of the observations seems worth while at this time.

The first patient of this group, *case 1* is an energetic woman in her middle thirties, highstrung, and a participant in a variety of community activities. She complained of severe throbbing headache the onset of which could be expected regularly 6 days premenstrually. The headache persisted with varying intensity until the 2nd or 3rd day of the menstrual flow. During this period of constant headache, the patient experienced fears, chiefly of impending catastrophe, either to herself or to her family. The headaches and fears were of such intensity as to prevent her from carrying on, not merely the variety of social duties to which she was committed, but even the routine household chores which usually she could dispose of in an hour or two. The complaint was of nearly a year's duration at the time when she was referred for study. During the year she had tried to relieve herself by employing one after another of the usual variety of headache remedies ranging from aspirin in heroic doses through the more complicated antidolorosum compounds. She had also consulted several physicians and had undergone an extensive physical examination which ruled out the organic lesions most frequently responsible for headaches of such intensity.

Menarche had occurred at 14.5 years of age. The periods had initially been profuse, with 6 days of flow every 26 or 27 days. There was occasional dysmenorrhea. She had married at 26 and had one child 2 years later. Since the birth of the child she had used contraceptives. She had noticed that during the past 2 years the periods had become a little scantier and spaced a little further apart. The flow was now 4 to 5 days every 29 to 30 days. Physical examination revealed no abnormalities.

Because of the association of the headaches with the menstrual period, vaginal smears were made daily and studied. Post-menstrually there was the usual progressive increase in cornification of the vaginal epithelial cells. On the 13th day the change associated with ovulation was noted. Epithelial desquamation and folding of the cells in the smears of the post-ovulative phase, which is characteristic of progesterone and estrogen activity, continued to occur in the normal manner for 7 more days. On the 20th day of the cycle, she reported that on her way to the hospital for the examination she had had serious misgivings that she would have an accident. The vaginal smear on that day consisted of cell types 7-1-8 (1), indicative of an abnormally low hormone level in a woman not yet in the menopause. Headache began in the evening. On the next day the vaginal smear was essentially the same. The patient feared she would be unable to continue her daily visits, for she was usually confined to bed for most of the pre-menstrual week. Since the smears indicated so low a hormone level, it was considered worth while to test the effect of an estrogen supplement. Accordingly, 1 mg. of estradiol dipropionate[2] was given intramuscularly. On the next day she appeared, wearing a new dress and a new smile. She reported that 4 or 5 hours after the injection she had begun to feel elated. The headache faded to a dull heaviness which no longer bothered her. She shopped in the afternoon and visited friends in the evening. The smear consisted of cell types 7-1-(2) (1), indicating a slight elevation in estrogen effect. The estrogen level continued to increase slightly during the next 4 days and then began to diminish gradually. Menses began on the 28th day of the cycle. The patient was free from headache and from phobia during the entire period with no further

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[2] The estradiol dipropionate, Di-Ovocylin, was supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

therapy. In subsequent months, she received varying doses of estrogens, in an attempt to discover the minimal effective dose and the optimal dose. During a vacation, a month without therapy, there was a recurrence of the symptoms, with their usual severity.

The second patient, *case 2*, was referred by a psychiatrist. Further endocrine study was requested because the results of a general physical and gynecologic examination were negative, and there was a history of progressively scantier menses. Vaginal smears made daily were normal until the 18th day of the cycle. At that time there was a regression of the cell types, with the gradual appearance of cells from the deeper layers of the vaginal mucosa. On the 23rd day of the cycle a few *type 8* cells were first noted. Headaches associated with hunger began 2 days later, when the vaginal smear showed 7-8-2 (1) indicative of an abnormally low hormone level for so young a woman. On the basis of the experience with the previous case, 1 mg. of estradiol dipropionate was adminstered. The next day the patient reported an absence of abnormal hunger, even some revulsion at the smell of food, and a marked reduction in the severity of the headache. The vaginal smears showed progressive cornification up to the time of menstruation which began on the 31st day. The flow was scanty, consisting of but one gush of bright red blood followed by spotting for two days. In the second month the vaginal smears showed essentially the same pattern as before. On the 27th day, 3 days after *type 8* cells had first been noted in this cycle, the patient again complained of both headaches and hunger sensations. Twenty gm. of glucose was administered intravenously after blood had been drawn for a fasting blood-sugar determination. The glucose relieved the hunger sensations only for 30 minutes, and the headache grew progressively more severe. One mg. of estradiol dipropionate and 5 mg. of progesterone[2] were administered together intramuscularly. The patient reported immediate relief of symptoms, much more complete than when estradiol alone had been given the month before. Indeed, the promptness of response was such as to suggest that the effect of the injection might have been psychic. However, menses began 3 days later with only a slight backache; the flow was more profuse than it had been for several years. It was of 3 days' duration with spotting on the 4th day. In the 3rd month, on the 26th day, she was given a placebo injection intramuscularly. The headache failed to respond to the placebo. The next day, with symptoms increasing in severity, she was given 5 mg. of progesterone-in-oil, intramuscularly; but this without the estradiol was ineffective. She reported an increased severity of the headache and increased hunger pains. Menses which followed 3 days later resembled that of the preceding month. In subsequent months she has been receiving 0.1 mg. of diethylstilbestrol per day during the last two weeks of each cycle. This therapy is more practicable than the estradiol and progesterone injection and serves to control the headache and hunger moderately well. It has made the menses somewhat more profuse than before therapy was instituted. The average duration of flow during the past 3 months has been 2.5 days.

Case 3 is a professional woman, married and in the latter thirties. Like the other patients, she is a nervous, highstrung, active woman trying to do two jobs at once. She was referred as a sterility problem. The vaginal smear pattern was essentially normal, except that the smears of the pre-menstrual week resembled those of women in menopause. The injection of 0.5 mg. of estradiol dipropionate intramuscularly about 1 week premenstrually prevented completely the occurrence of incapacitating headache. Therapy with diethylstilbestrol failed. Since receiving therapy she can carry on her work more efficiently and effectively than before. This therapy has been continued for 6 months.

Case 4 is precisely like *case 3* except that the patient was referred specifically because of premenstrual headaches, and the headache has been successfully controlled for 5 months, by a single injection of 0.5 mg. of estradiol dipropionate given a week premenstrually.

Case 5 is an unmarried professional woman, 29 years old. Menarche had occurred at 14.5 years. Her next menstrual period came when she was 16 years old. The onset of the premenstrual headaches dated from about age 21, when she had had an episode of serious menorrhagia requiring surgical intervention, and transfusion. This never recurred. About 8 years ago, on the day preceding menses and during the past 2 years, for 4 or 5 days preceding menses, she had had severe left-sided headaches beginning over the occiput and radiating into the left eye. At times she felt 'half blinded.' During the last year she had had to spend 2 or 3 days of each month in bed, and had been given morphine on several occasions to control the pain. When menstrual flow began the headache disappeared. Vaginal smear study revealed that ovulation occurred on the 7th day of the cycle. There was a normal post-ovulative cell pattern in the smears following the usual course for about 12 days. Fragmented cells, but no red blood cells then became the predominant characteristic of the vaginal smear picture, indicating a very low hormone level. The vaginal smear remained essentially unchanged until menses occurred on the 29th day. In the second cycle, diethyl-

[2] Progesterone (Lytocylin), was supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

stilbestrol,[4] 0.5 mg. per day, was given starting about 10 days before the expected menses. The patient experienced transient nausea on the second day of medication. Headache did not occur. The vaginal smear studies revealed the effect of the estrogen dosage. The epithelial cells were types 2-7-3(1). Menstruation occurred a day sooner than expected, on the 17th post-ovulative day, the 27th day of this cycle. The flow was somewhat more profuse than usual, but otherwise was not remarkable. This schedule of therapy has been used for 4 months without further recurrence of headaches.

Case 6 was seen in the course of only 2 months. She had had very thorough examinations by competent physicians elsewhere. She is a woman in her early forties, supporting herself and her family. For the past 5 years she had noticed that the menses had become more scanty. Premenstrual headaches had been growing progressively more severe untill they threatened to impair, if not, disrupt her ability to earn a living. She was first seen on the first day of a headache, the 22nd day of that cycle. The vaginal smear on that day was typically pre-menopause containing cell types 2-7-8(1). She was given 1 mg. of estradiol dipropionate intramuscularly and was asked to report results a week later. She reported that the injection aborted the mild headache and that during the premenstrual week she felt better than she had 'for 10 years before.' In the second cycle she was given diethylstilbestrol, 0.1 mg. a day, starting on the 16th day of the cycle. This medication controlled the severity of the headache but failed to prevent it completely. Further experiments with timing and dosage will be required in order to find the optimal therapy for this patient.

DISCUSSION

The need for estrogen in 6 relatively young women with active ovarian function suggests that gonad hormone production may fall below physiologic requirements, despite maintenance of menstrual function. This observation should be considered together with the evidences that continued ovarian function may persist even after cessation of menses. Thus, just as the period of adolescence is protracted, and the menarche by no means represents complete maturity of reproductive capacity (2, 3), so the loss of reproductive capacity must be considered a gradual process. In most women, the approaching menopause is heralded by scantier menses and longer intermenstrual intervals. In a few women, 'menopausal' symptoms may develop despite little change in the character of the menses. It is probable, in the light of our psychosomatic investigation (4, 5) that those women whose environment demands severe nervous integration and coördination will suffer most from lack of estrogen. This hypothesis fits well with the fact that all 6 of these patients are active, highstrung, nervous women engaged in work outside the home.

The 6 cases reveal certain similarities, *a*), severe, incapacitating premenstrual headache; *b*), nervous, highstrung, active women; *c*), childbearing age; *d*) vaginal smears consisting predominantly of fragmented cells (*type 7*) and cells from deep layers of the mucosa (*types 1* and *8*); i.e., the premenstrual phase presents smears indicative of a relatively atrophic vaginal mucosa and suggests the existence of an abnormally low gonad hormone production; such smears are never found in young adult women unless there is vaginitis; *e*) prompt amelioration of the symptoms occurring with moderate estrogen dosage; *f*) dosage and timing of the therapy seem to require individual adjustment, although in the cases so far studied, 1 mg. of estradiol dipropionate intramuscularly about a week before the onset of menses is adequate, if not optimal.

Many more patients suffering from severe premenstrual headache should be carefully studied to determine the validity of the syndrome. The vaginal smear technique is a useful and practical diagnostic aid for this purpose.

I wish to acknowledge with thanks the assistance, advice and criticism of Dr. S. Soskin, Director of the Department of Metabolism and Endocrine Research, Michael Reese Hospital, Chicago, Ill.

[4] The diethylstilbestrol was supplied by Dr. E. G. Upjohn, of The Upjohn Co., Kalamazoo, Mich.

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Ethinyl Estradiol: A Clinical Evaluation

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THE QUEST for an orally effective estrogen has occupied the attention of chemists for the past decade. This search has been greatly accelerated during the past few years, and remarkable results have been obtained, particularly in the production of non-steroid compounds that possess great estrogenic activity. Of this group, diethylstilbestrol is very potent and does not lose its effectiveness on oral administration. The natural estrogens, when taken orally, are comparatively ineffective. This has been shown to be due to inactivation by the liver (1). Hohlweg and Imhoffen (2) prepared ethinyl estradiol which, although a natural estrogen, is active on oral administration. They report that it is 15 to 20 times as effective as estradiol when taken by mouth. The presence of the ethinyl radical probably protects the estrogenic activity of the compound, either from destruction in the gastro-intestinal tract or from inactivation by the liver. Preliminary investigation of the activity of this compound in castrated female rats, by the method used previously in the study of estrone and estradiol, has shown that in comparable amounts, the liver is not able to inactivate ethinyl estradiol (3). There have been very few reports on the clinical use of ethinyl estradiol (4); the following is an analysis of the results observed in 33 menopausal women.

METHOD OF INVESTIGATION

Of the 33 cases studied, 20 had undergone a natural and 13 an artificial menopause. All complained of the usual symptoms: flushes, sweats, headaches, dizziness, numbness of the extremities, arthralgias, excessive fatigue, insomnia and nervousness. In both groups the severity of the symptoms varied considerably, and in general the surgical castrates presented the most severe symptoms. It was possible to study many of the patients for periods as long as 2 years.

Minimal doses of the ethinyl estradiol[1] were used in all instances. The preparation was originally supplied in tablets containing 0.15 mg. and later, as tablets containing 0.05 mg. When ethinyl estradiol was first employed the majority of patients was given 0.15 mg. daily for a period of 14 to 21 days, and the dosage was then decreased to 0.15 mg. every other day. In a few instances 0.30 mg. was the initial daily dose and this was gradually decreased after 7 to 14 days. It was found that this latter large dosage alleviated symptoms within 4 or 5 days. Most of the symptoms were completely relieved in 7 to 10 days. Later it was found that if 0.05 mg. was taken 2 or 3 times daily and the dosage slowly decreased to once a day the symptoms were controlled. Those women who were passing through a natural menopause, as a rule, required less medication, and frequently could stop using the drug for several weeks at a time. With the reappearance of symptoms the patients returned for further therapy.

Our evaluation of the therapeutic effectiveness of this new compound in the treatment of the diverse symptoms of the menopause is based mainly on its ability to control the symptoms; its estrogenic activity is of secondary importance. For this information we were directly dependent on the reactions of the patients to the drug, and we attempted to interpret these as objectively as possible. The major symptoms, the flushes, sweats, headaches and dizziness, in all but 4 instances, disappeared in 7 to 10 days and remained in abeyance as long as administration of the drug was continued. In two cases there was but moderate control of symptoms. When an occasional flush occurred the patients stated it was mild and tolerable. There was a marked improvement in the general well being of all these patients. It was noted that with symptoms well controlled on adequate therapy that a physical or psychic upset would induce a recurrence of flushes and sweats.

Vaginal smears. Smears stained by the method of

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[1] The ethinyl estradiol used in this study was supplied through the courtesy of Dr. William R. Bond of the Schering Corp., Bloomfield, N. J.

Salmon and Frank (5) were made at regular and frequent intervals on all cases. The changes in the smears did not always parallel the course of clinical improvement. A cornification of the vaginal epithelium is generally expected to accompany symptomatic relief, but often the cells in the smear remained the same in appearance or changed slightly, and in many instances the smear continued to show yielded merely a mixture of blood and mucus. After the treatment with ethinyl estradiol was well under way endometrial tissue could be obtained more easily from these patients. These biopsies in most instances showed the endometrium in the proliferative stage, and some specimens revealed a marked hyperplasia with dilated and cystic glands. The histologic picture was characteristic and concurs in all respects with

TABLE 1. DATA ON MENOPAUSAL PATIENTS TREATED WITH ETHINYL ESTRADIOL

Case and Name	Age, yr.	Occurrence of Last Menses	Type of Menopause	Period of Treatment	Type of Endometrium	Bleeding During Treatment	Total Dosage mg.
1, Mrs. S. F.	45	3½ years ago	Natural	12/28/40–6/15/42	11/8/41; Cystic hyperplasia 2/26/42; Proliferative	Intermittent episodes of bleeding finally resulting in curettage on 2/28/42	33.0
2, Mrs. A.P.	44	Regularly recur every 5–6 weeks	Natural	12/28/40–4/19/41		None	7.2
3, Mrs. P.V.	45	3 years ago	Natural	8/3/40–6/7/41		None	9.15
4, Mrs. T.T.	57	2½ years ago	Natural	1/4/41–2/18/41		None	6.75
5, Mrs. E.S.	48	Regular recurrence every 28 days	Natural	8/31/40–7/9/42	9/14/40; No tissue obtainable	Slight spotting	14.1
6, Mrs. A.G.	48	3 months ago	Natural	1/25/41–3/22/41	1/25/41; Secretory	None	6.45
7, Mrs. A.S.	57	10 months ago	Natural	11/2/40–3/1/41	11/2/40; No tissue obtainable	None	8.25
8, Mrs. A.G.	58	8 years ago	Surgical	2/15/41–4/15/41		None	6.15
9, Mrs. R.P.	39	5 years ago	Surgical	8/3/40–2/27/41		None	9.75
10, Mrs. A.B.	33	12/10/40	Surgical	1/25/41–7/9/42	8/14/41; Proliferative 9/15/41; Proliferative	Fairly regular periods with occasional episodes of prolonged bleeding	49.05
11, Mrs. P.K.	42	Regular recurrence every 30 days	Natural	2/27/41–6/12/41		Slight spotting	7.05
12, Mrs. M.B.	43	1 year ago	Surgical	12/21/40–5/3/41		None	12.30
13, Mrs. E.F.	52	May, 1940	Natural	10/5/40–7/16/42	10/5/40; Resting 8/14/41; Secretory phase	Fairly regular periods about every 2 months	30.15
14, Mrs. S.K.	43	Regular recurrence every 26 days	Natural	4/10/41–5/24/41		None	5.1
15, Mrs. B.F.	51	3 months ago	Natural	11/6/40–10/11/41		None	12.3
16, Mrs. E.B.	47	March, 1940	Surgical	12/28/40–7/9/42		None	38.4
17, Mrs. B.G.	42	December, 1940	Natural	2/8/41–6/26/41	2/18/41; Proliferative	None	6.9
18, Mrs. T.P.	49	1937	Surgical	8/3/40–8/14/41		None	8.1
19, Mrs. S.B.	50	April, 1941	Natural	4/27/41–6/25/42	7/10/41; Proliferative	Spotting and slight bleeding at irregular intervals	12.6
20, Mrs. L.N.	35	April, 1941	Surgical	8/31/40–9/25/41	9/5/41; Proliferative 9/18/41; Proliferative	Profuse, prolonged bleeding	6.75
21, Mrs. B.K.	46	April, 1941	Natural	12/18/41–8/27/42		Profuse, intermittent bleeding	8.4
22, Miss A.F.	45	February, 1942	Surgical	4/9/42–8/27/42		None	12.9
23, Mrs. R.B.	43	December, 1941	X-ray	3/7/42–5/28/42	3/7/42; No tissue obtainable	None	13.5
24, Mrs. I.B.	42	December, 1941	Surgical	3/26/42–8/20/42		None	8.4
25, Mrs. B.G.	45	Irregularly recur every 6–8 weeks	Natural	5/12/41–6/8/42	3/27/42; Proliferative	None	12.6
26, Mrs. E.B.H.	52	Regular recurrence every 28 days	Natural	9/18/41–8/27/42		Slightly prolonged period	18.9
27, Mrs. J.M.	40	Irregularly recur every 6–8 weeks	Surgical	2/4/41–6/18/42	6/13/41; Proliferative	Profuse, intermittent bleeding	21.3
28, Mrs. J.K.S.	40	May, 1936	Surgical	10/24/41–1/17/42		None	8.4
29, Mrs. U.R.	52	Regular recurrence every 5 weeks	Natural	8/7/41–5/21/42		Slight spotting	12.3
30, Miss G.R.	53	5 years ago	Natural	9/9/41–4/20/42		None	11.4
31, Mrs. M.S.	45	Irregularly recur at 28-day intervals	Natural	8/10/40–8/17/42	9/15/41; Proliferative	Profuse, intermittent bleeding	25.2
32, Mrs. C.H.	45	4 years ago	X-ray	7/2/41–7/30/42		Slight bleeding	18.7
33, Mrs. J.D.	39	6 years ago	Surgical	9/12/40–7/21/42		None	38.4

atrophy cells. It is assumed that if large doses of ethinyl estradiol were given it would have been possible to convert the atrophic vaginal mucosa to the mature type; however our object was to obtain symptomatic relief.

Endometrial biopsies. Whenever possible biopsies were obtained from the patients in the Outpatient Department in order to study the endometrial changes. Obtaining biopsy specimens without an anesthetic is a painful procedure in some instances. Nevertheless it was done as often as possible in suitable cases, especially in multiparas on whom the cervical canal was easily dilated. We have found it difficult to obtain satisfactory endometrial tissue in the menopausal patient who has not menstruated for several months or years. Repeated attempts at biopsy reports in previous papers on the effects of other estrogens on the endometrium.

Several undesirable effects were noted during the period of treatment which are worthy of discussion. The first two were expected and their appearance caused no surprise.

Bleeding. The presence of proliferative endometrium in many of the cases was accompanied by slight or marked bleeding in 5 instances. Several patients in this series who had not menstruated for years were both alarmed and surprised when flowing again. Others have had marked bleeding over a period of 10 days which subsided to a slight flow lasting for 7 to 14 days. In one instance bleeding continued for 35 days and was accompanied by severe cramps and lower abdominal pain. It was necessary to admit this

patient to the hospital for a curettage. The endometrium was hyperplastic and its removal was followed by a cessation of the bleeding.

Bleeding was reported by the patients during the period when they were taking the drug. In several ovariectomized patients, in whom the uterus was still present, the bleeding was almost cyclic in its recurrence and character during treatment. Withdrawal bleeding occurred in one instance. No attempt was made to treat this bleeding with other agents.

Leukorrheal discharge. Several patients complained of the appearance of a white discharge. This symptom was apparently due to the increased maturation and cornification of the vaginal epithelium as a direct result of the specific treatment.

Headaches. Three patients suffered from severe headaches which can be attributed to the effects of the drug. In two instances the headaches subsided while the treatment was continued; one lasting 14 days, the other 3 days. In the third instance it was necessary to discontinue the use of the compound after 2 weeks during which time the headaches persisted.

Nausea and vomiting. The patients were under constant observation for these and related symptoms which commonly occur during diethylstilbestrol therapy; however, they did not manifest themselves.

Most of the patients studied were able to take ethinyl estradiol with excellent results and without unusual symptoms or side effects being noted. Two cases which were especially interesting are reviewed briefly.

CASE REPORTS

Case 1. Mrs. S.F., age 45 years. This patient was an extremely emotional, nervous woman who had had several major operations. She had been a chronic invalid for years. She complained of flushes, sweats, insomnia, nervousness, headache, dizziness and amenorrhea of 3½ years duration. Her response to ethinyl estradiol was dramatic, with a prompt disappearance of the symptoms within 7 days.

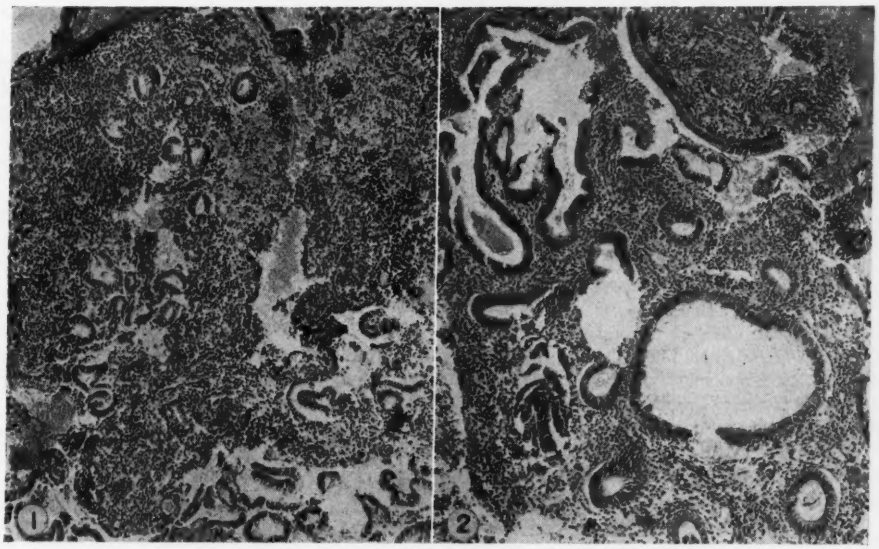

Fig. 1. Fragments of endometrium composed of uniformly small glands widely spaced in an edematous stroma; case 1.
Fig. 2. Endometrium, showing extreme variation in size and shape of glands with some undergoing cystic dilatation; case 1.

Beginning on Dec. 28, 1940, a dosage of 0.30 mg. of ethinyl estradiol daily was given. This was reduced to 0.15 mg. after 10 days. Catamenia lasting 8 days began on Feb. 3, 1941. This was the first period of flow in 3½ years. On May 17 flowing appeared and lasted for 1 day. The patient had been feeling unusually well. On August 20 flow began and continued for 14 days. The patient had been enjoying excellent health, was less nervous and seeking employment. On October 18 she reported there had been no bleeding since September 3. She was enthusiastic about the way she was feeling, and she was employed at this time. The normal resting endometrium shown in figure 1 was obtained from this patient. On November 13 a slight flow began lasting for 4 days. On December 3, twenty-one days later, a moderate continuous flow lasting for 9 days began. Six weeks later, on Jan. 13, 1942, a 4-day catamenia began which was accompanied by moderately severe cramps. Figure 2 shows the cystic hyperplasia of the endometrium in this case. On Feb. 12, 1942, the patient reported a continual flow accompanied by lower abdominal pain. By February 28 this had become a profuse bleeding

and she was hospitalized for curettement. This was performed under gas anesthesia and she was discharged after 48 hours. On April 8, 1942, she reported there had been no bleeding since her discharge from the hospital.

Case 10, *Mrs. A.B.*, age 33 years. The patient is known to have had diabetes since 1930. She had had two abdominal operations, the first in April, 1940, at which time the right tube and a cystic ovary were removed. In December of the same year a second operation was performed for an ectopic pregnancy which was complicated by a massive hemorrhage. Within a week following the second operation she complained of marked flushes and sweats. She was given 0.30 mg. of ethinyl estradiol daily, beginning on Jan. 25, 1941, and she has continued to take it in varying dosages until the present time. The response to treatment with ethinyl estradiol has been gratifying. The flushes and sweats disappeared and she stated that she felt like her usual self. Her weight increased from 161 to 177 lb. During January and February of 1942 the average dosage of ethinyl estradiol was 0.05 mg. per day.

The cycles of bleeding which have recurred since the second operation are of interest in view of the fact that both tubes and ovaries had been removed. The first episode of flowing after initiation of treatment on January 25, was on March 2. The amount was scanty and lasted but 1 day. A normal flow of moderate amount lasting for 3 days began on March 29, 28 days after the previous 1-day period. On June 7 a 4-day period began after an interval of 70 days. The flow was heavy and associated with lower abdominal cramps. After an interval of 24 days a 3-day period began on July 11, which was followed in turn by an interval of 9 days; a scant flow lasting 2 days began on July 19. Sixteen days later, on August 4, a scant flow started which lasted for 3 days. A scant flow, lasting for 1 day, appeared on August 24, after a 21-day interval. Thirty-four days later, on September 27 there was a moderate flow of 4 days' duration. On October 20 spotting appeared for 1 day after an interval of 24 days. Sixty-six days later, December 24, a scanty flow associated with a few crampy pains appeared and lasted for 2 days. On Feb. 10, 1942, a moderate flow of 5 days' duration began after an interval of 49 days.

DISCUSSION

During the past few years the development of oral estrogenic therapy has provided an economical method for treating menopausal patients. This has become increasingly important since it is obvious that estrogenic therapy is substitution therapy and often must be continued for months or years. Numerous preparations, of which diethylstilbestrol and its derivatives are the most effective, have been tried. None has proved entirely satisfactory owing either to lack of potency on oral administration, or to various untoward side effects. The use of diethylstilbestrol, the most potent oral compound available, which singularly enough is not a steroid, is often attended by nausea and vomiting and this militates against its use in many cases (6). The development of an orally effective steroid estrogen, ethinyl estradiol, which in our hands has shown practically no toxic symptoms, is a welcome advance. Little is known concerning the metabolism of diethylstilbestrol or the mechanism of its ultimate disposal by the body, except that it may not be inactivated by the liver in the manner estrone and estradiol are (3). Estradiol on the other hand, is a natural product of glandular metabolism, and its synthetic ester, ethinyl estradiol, is more likely to be assimilated and catabolized by the body with fewer untoward reactions. The recent observations on the control of the inactivating function of the liver by vitamin B complex (7, 8), suggests that the minor side effects related to the administration of this compound may be relieved by giving the vitamin with it.

SUMMARY AND CONCLUSIONS

Ethinyl estradiol was administered orally to a group of 33 menopausal women. The dosage varied from 0.05 to 0.15 mg., given one to 3 times daily. Excellent control of symptoms occurred in 27 cases, moderate control in 2 cases, and in only 4 cases was the drug ineffective. Vaginal smears and endometrial biopsies in most of the cases showed changes compatible with estrogenic activity after variable periods of therapy. Vaginal bleeding during therapy appeared in 7 cases; withdrawal bleeding occurred on cessation of therapy in one case. During treatment 3 patients complained of headaches; in one it was sufficiently severe to necessitate discontinuing treatment, in the other two the headaches disappeared. Nausea and vomiting did not occur. This new oral steroid estrogen, ethinyl estradiol, has shown great effectiveness in controlling the symptoms of the menopause. The toxic manifestations that have been described with the nonsteroid oral estrogens did not occur.

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Male Hypogonadism: Effect of Treatment on Genital Growth and Maturity

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METHYL TESTOSTERONE is a potent androgen which is orally effective. Clinical experience with substitution therapy (1–31) in male hypogonadism has produced generally satisfactory, but not always completely successful results. The technique of medication, criteria for dosage and the possibility of producing side effects require further elaboration. A comparison of the results reported with those of a new, and previously untried, concentrated preparation of testosterone propionate inunction is of interest. Finally, variations in the initial clinical picture of the hypogonad male and of his response to treatment deserve further emphasis in order to facilitate a more accurate prognosis in a given case.

MATERIAL, MEDICATION AND METHOD

This report concerns the effect of male hormone administration in 9 hypogonad males over 18 years of age, 8 of whom also displayed a marked hypogenitalism. The subjects have been observed over a period of 4 months to 2.5 years. All were examined from a systemic and metabolic point of view, including routine laboratory studies of the urine and blood for formed elements and serologic reaction, determination of the basal metabolic rate, serum cholesterol, calcium, phosphorus and sugar tolerance as well as roentgen visualization of the skull, sella turcica and epiphyseal maturity. The clinical study generally followed lines already previously described. Brief condensations of pertinent information regarding initial findings, medication and results are tabulated in table 1.

Methyl testosterone,[1] containing 10 mg. of the active substance per tablet was given orally, with a little water, once daily, at bedtime. Abstinence from food for the preceding 4 hours appeared to promote the action of the drug, while administration at the time of retirement provided an optimal period of body relaxation to gauge the maximal stimulation overnight and on arising. The occurrence of nocturnal or morning erections varying in frequency from once or more in 24 hours in the early phases of treatment to several times per week later, served as the criterion for the adequacy of the dosage. An average of 10 to 30 mg. daily appeared to be sufficient for this demonstration of physiologic effectiveness.

A testosterone propionate inunction[1] containing 25 mg. of the active substance per gm. of the base was later substituted for oral therapy over a period of 3 months in 4 of the cases of hypogonadism and hypogenitalism. The ointment was applied at bedtime to the lower abdomen or inner aspects of the thigh and rubbed thoroughly into the surface without preliminary preparation of the skin. In some instances the ointment was also applied directly to the penis or to the areas of potential hairgrowth in an effort to promote local effects. A daily dosage of 12.5 mg. of androgen percutaneously seemed comparable in its effectiveness to twice the amount of methyl testosterone orally as judged by the criterion described. Percutaneous application was no more troublesome than the oral route.

Progress in the stimulation of penile growth was determined by the increase in the length of the organ both in the relaxed and erectile state. Measurement of the relaxed organ did not appear to be entirely satisfactory because of its retractile properties depending upon the tone of the smooth muscle, the autonomic nervous system and temperature, which vary with constitutional differences between individuals, as well as in a given individual from time to time. A more constant and dependable figure was obtained during erection. This method of measurement has the additional merit of including an index of total penile vascular capacity. Normal individuals differ considerably in this genital 'co-efficient of expansion.' The short and stocky type may attain an erection 4 to 5 times that of the initially short penile contractile length, while in a slender-boned, leptosome with pendulous genitalia, the increment may be less pronounced. The relaxed length from base to

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[1] The methyl testosterone and the testosterone propionate inunction were supplied by Dr. E. Oppenheimer, Dr. R. McBrayer and Mr. L. H. Neil of Ciba Pharmaceutical Products, Inc., Summit, N. J.

tip of the glans was recorded by the physician while the spontaneous erectile length, usually available before the first morning voiding, was similarly measured by the patient. Although open to the criticism that the latter process necessitated the acceptance of data collected by the patient and that, therefore, it is sub-

TABLE 1. CLINICAL DATA IN HYPOGONAD CASES

Case No.	Clinical History	Medication	Months of Observation	Wt., lb.	Ht., in.	Genital Length, in.		Genital (Pubic Hair) Maturity	Observation	Comment
						Relaxed	Erectile			
1, P.W.; age 19 yr. Observation period 21 mo.	Cryptorchid and hypogenital at 10. Few pubic hairs at 16. Severe fatiguability. Impulse poorly sustained. Emotional lability. Excellent intelligence. Sex curiosity toward females. No contacts. College student. Configuration fleshy with long extremities. Autonomic instability. Parents average build. No endocrine disease	None	Initial	140	66.4	0.5		trace	Fig. 1, A. Left testicle in external ring. Surgery one year later, fibrous tissue	Hypogonad. Libido and neurovascular irritability well maintained throughout with treatment. Genital growth excellent up to full pubic hair thickness, none following. Skeletal response with maturation
		Testosterone propionate inunction, 14 mg. daily	2			1.5	2.5	1+		
		Methyl testosterone, 40 mg.	3		67.5	2.5	3.5	2+	Fig. 1, B. Voice deepening	
		None	3		68.4	3.0	4.5	4+	Fig. 1, C. Voice deep. Severe acne	
		20 mg.	10	157	69.6	3.0	4.5	4+	Axillary hair. Broadening of bones	
		Testosterone propionate inunction, 25 mg. daily	4	155	71.0	3.0	4.5	4+	Epiphyses open. No facial hair	
2, G.R.; age 28 yr. Observation period 27 mo.	Cryptorchid and hypogenital at 14. Minimal pubic hair development, 20–25 yr. Tall, big boned, progressive obesity. Hard working, ambitious, even-tempered. Good intelligence. Machinist. Normal sex curiosity but no contacts. Parents and 5 brothers tall and big-boned.	None	Initial	263	70.0	0.5		1+	Fig. 2, A. Both testes pea-size, soft, insensitive. No sperm	Hypogonad. Libido and neurovascular irritability of penis well maintained with treatment. Genital growth good up to almost full pubic hair thickness; none since.
		Testosterone propionate injection, 25 mg. 3x weekly	4			2.5	4.5	2+	Fig. 2, B. Fewer erections	
		Chorionic gonadotropin 1,000 I.U. 3x weekly injection	4			2.5	4.5	2+	Fig. 2, B. Fewer erections	
		Methyl testosterone 50–100 mg. orally	7	208	70.0	3.0	5	3+	Fig. 2, C. Voice deep. Axillary hair appearing. No facial hair. Sex interest. Dancing. Weight loss through diet.	
		30 mg.	9	210	70.0	3.0	5	3+		
		Testosterone propionate inunction 12.5 mg.	3	203	70.0	3.0	5	3+	Scattered chin hairs	
3, J.H.; age 18 yr. Observation period 21 mo.	Cryptorchid and no pubic hair at 15. Completely atrophic testes removed surgically. Tall, slender-boned, athletic. Good impulse, even-tempered, good intelligence. Good student. Normal sex curiosity but no contacts. Parents normal, tall	None	Initial	120	68.9	1.0		0	Fig. 3, A. Testes not present.	Hypogonad (castrate). Libido and neurovascular irritability well maintained with treatment. Genital growth good up to almost full pubic hair thickness, none since. Good skeletal and muscle response.
		Chorionic gonadotropin, 1,000 I.U. 3×weekly injection	3	121	69.0	1.0	1.5	0		
		Methyl testosterone, 40 mg.	3	146	70.0	3.0	4	1+	Fig. 3, B. Voice breaking	
		30 mg.	12	147	72.3	3.0	4.5	3+	Fig. 3, C. Voice deep. Moderate axillary hair but none on face	
		Testosterone propionate inunction, 12.5 mg.	3	148	72.2	3.5	5	3+	Epiphyses open	
4, E.S.; age 18 yr. Observation period 26 mo.	Genital hypoplasia through childhood. Pubic hair at 15. Weak to no sex interest. Tall, broad-boned, Weak in impulse; sensitive, irritable. Dull intelligence, retarded in school. Parents tall, broad-boned. Mother tall, hypogonad, hysterical psychopath.	None	Initial	214	67.9	1.5	3	3+	Testes bean-size	Hypogenital and some hypogonadism, mild. Libido and neurovascular irritability good with treatment. No genital growth response with beginning of therapy near full pubic hair thickness.
		None	14	197	68.7	1.5	3	4+	Testes olive-size. Normal sperm	
		Methyl testosterone, 40 mg.	6	204	69.9	1.5	4	4+		
		20 mg.	3	210	70.5	1.5	4	4+	Fig. 4. Voice now deep. Some facial hirsutism. Testes firm. Interest in opposite sex	
		Testosterone propionate inunction, 12.5 mg.	4	215	70.0	1.5	4	4+	Testes olive size. Normal sperm	

TABLE 1. CLINICAL DATA IN HYPOGONAD CASES—*Continued*

Case No.	Clinical History	Medication	Months of Observation	Wt., lb.	Ht., in.	Genital Length, in.		Genital (Pubic Hair) Maturity	Observation	Comment
						Relaxed	Erectile			
5, *R.M.*; age 20 yr. Observation period 20 mo.	Cryptorchid at 12. Rt. testicle rudimentary in scrotum at 15, with first appearance of pubic hair. Broad-boned, long extremities, wide pelvic bones. Ambitious, sensitive, mood swings to mild depressions, excellent intelligence. College student. Normal sex interest toward females and trial experience. Parents normal.	None	Initial	165	65.0	0.5	1.5	3+	Rt. testicle only palpable; bean size	Hypogonad. No genital growth response with beginning of therapy near full pubic hair thickness.
		Chorionic gonadotropin, 1,000 I.U. 3×weekly injection	5			1.0	1.5	4+	No enlargement of testis which softened. Axillary hair present. Voice breaking	
		Testosterone propionate injection 25 mg. 3× weekly	12	168	66.2	1.0	2.5	4+	Voice deep. Shaves once per week. No spermatozoa	
		Methyl testosterone, 30 mg.	3			1.0	2	4+	No further change. Fig. 5.	
6, *J.B.*; age 20 yr. Observation period 4 mo.	Pubic hair first at 14. Testes always barely palpable. Normal asthenic configuration. Progressive body hirsutism. Impulse life weak. Anxious, worrisome temperament. Ego-sensitive with marked compensation. Dull, average intelligence. Interest in opposite sex social only. Masturbation. Parents normal leptosomes	None	Initial	140	72.0	1.0	4	4+	Testes soft, pea to bean-size. No spermatozoa. Pronounced hirsutism. Shaves daily. Voice normal	Hypogonad. No genital growth response with beginning of therapy after full pubic hair thickening.
		Methyl testosterone, 30 mg.	4	142	72.0	1.0	4	4+	Fig. 6. Testes soft, rudimentary. No change. Increase in libido, aggressiveness and optimism	
7, *A.W.*; age 28 yr. Observation period 4 mo.	Cryptorchid on rt. Left testicle small, in scrotum at 14 with first appearance of pubic hair. Tall, broad boned with progressive obesity especially abdominal and chest. Marked gynecomastia. Impulse poor, minor depressions, good intelligence. Interest in opposite sex but superficial contact only. Salesman. Parents obese.	None	Initial	269	67.4	1.0	2	3+	Left testicle pea-size, soft. Facial hair present. Shaves once per week. Chest hirsutism. Pronounced gynecomastia. Androgenestrin ratio in urine low.	Hypogonad with secondary (compensatory?) adrenogenital syndrome. No genital growth response with beginning of therapy; near time of full pubic hair thickness.
		Methyl testosterone, 40 mg.	4	260	67.4	1.0	2	3+	No change except increase in libido and penile neurovascular irritability. Masturbation	
8, *P.H.*; age 31 yr. Observation period, 4 mo.	Pubic hair, genital size and testes normal at 15. Never developed axillary hair and only slight facial hair. Massive intrasellar pituitary tumor removed at age of 27. Radiation therapy later. Complete loss of libido. Divorce. Good energy, intelligence and normal skeletal build. Graduate student.	None	Initial	165	68.7	2.5	4.5	2+	Testicles olive size, firm. Shaves 2× weekly. No axillary hair. 17-ketosteroids, 10.1 mg. Gonadotropin, 0. Sella turcica 4×6 cm.	Hypogonad, secondary to pituitary deficiency. Genital maturation not improved with male hormone. Some genital growth.
		Methyl testosterone, 20 mg.	4	165	68.6	3.0	5	2+	No change in facial or pubic hirsutism. Libido and neurovascular irritability of penis normal with treatment	
9, *E.F.*; age 40 yr. Observation period, 6 mo.	Pubic hair first at 15. Testes normal. Typhoid fever. Facial hair never did grow well. Normal body build in skeletal and fat distribution. Pituitary infarction at 37. Addison's disease with crises. Response to desoxycorticosterone. Pituitary myxedema, (blood iodine, 2μg.) and hypogonadism. Loss of libido	None	Initial	125	65	2.0	3.5	2+	Testes olive-size. Soft. Shaves once per week. Voice normal. Severe secondary anemia.	Hypogonad secondary to pituitary deficiency. Pituitary myxedema and adrenal cortical deficiency. Genital maturation not improved with male hormone.
		Methyl testosterone, 5 mg.	4	125	65	3.0	4	2+	Response in libido and neurovascular irritability normal with treatment. Some genital growth. Troublesome priapism if dose of male hormone raised to 10 mg.	

ject to mistakes or exaggeration, the facility of the procedure and consistency of reports spoke well for its trustworthiness.

Of equal importance with the consideration of penile size and activity was the accurate observation of progression under treatment of qualitative changes

in the secondary sex characters, perhaps better designated as sex maturation. The participation of skeletal muscle, fat, mineral and water elements was clinically reflected in the alterations of height, weight and epiphyseal status. A most noteworthy manifestation, however, was the growth of hair on the various parts of the body.

The process of sex maturation is usually designated by the terms puberty, adolescence and maturity. Variations in the time required for sex maturation are well recognized. Some individuals develop from the status of children into fully mature men within a few years, while others may require 10 years or longer to negotiate the same transformation. The delay in

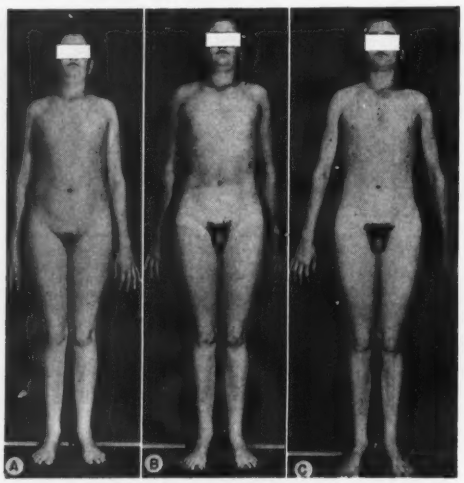

Fig. 1. Stimulation of genital growth and maturation in hypogonadism. *P.W.*, age 19. *A.* Prior to therapy. *B.* Five months after initiation of treatment with androgens. *C.* Eight months after initiation of treatment. Maximal genital growth attained prior to development of full thickness of the pubic hair.

the sequence of appearance of pubic, axillary, facial and chest hair may be increased. Extensions of the chest-hair growth frequently occur in men in their thirties and forties.

The period of pubic hair growth, from its first appearance to full thickening represents a most important and accelerated phase of the whole maturation process and, therefore, merits a special definition of puberty, namely, genital maturation.[2] More sharply localized in its onset, duration and age span of occurrence than the subsequent body hirsutism, the time of its development offers a valuable point of orientation for evidences of other body changes. Occurring usually within the limits of 11 to 16 years of age (more frequently 12 to 14) and varying with hereditary, racial and climatic factors, the actual onset may be timed closely within an accuracy of 3 months, by the appearance of coarse public hairs subsequent to a fine, downy accentuation clinging to the surface of the pubis for the preceding 6 months to a year. The maximal mass of public hair is usually attained within 2 years or less; full thickening is here denoted by a roughly quantitative index of 4+ and the halfway point, correspondingly as 2+. As will be shown, estimation of actual pubic hair thickening in terms of that maximally expected for the type of individual, is of clinical value in the establishment of prognosis for genital growth.

RESULTS

Genital functions. A rapid and most constant result of substitution therapy in male hypogonadism was the improvement of genital neurovascular and muscular functions. A rise in skin temperature, increased turgidity and irritability to spontaneous erection of the phallus became manifest within 48 hours. Maximal sensitivity to the hormone was noted in *a*) the younger age-groups, *b*) in individuals showing a greater degree of genital immaturity, and *c*) in one case of hypogonadism secondary to a pituitary and adrenocortical deficiency, in whom a single dose of 10 mg. of methyl testosterone at bedtime caused troublesome priapism overnight and next day. Generally, an average daily dose of 20 to 40 mg. of methyl testosterone was necessary for the maintenance of the desired neurovascular irritability, as well as the production of penile growth if this was to be attained at all.

Continuous and prolonged medication (over a period of 6 months) produced at times refractory periods during which spontaneous erectility disappeared while the libido and susceptibility to mechanical stimulations, as a masturbation, continued unimpaired. Rest for medication for one week appeared more effective in restoring spontaneous sensitivity than the stubborn continuation of the daily dose, or its increase to twice the previous level. Continuous dosage or over-dosage probably resulted in a waste of medication and at times also led to vague gastric distress.

In 4 cases the substitution of 12.5 mg. of testosterone propionate inunction (25 mg. of the active substance per gm. of base, applied at bedtime) for the oral type of therapy produced equally gratifying

[2] The terms genital maturation and pubic maturation are not identical. Genital maturation carries a broader connotation of a qualitative change of the genital tissues themselves. The term pubic maturation refers specifically to thickening of the pubic hair and is not identical with genital maturation, but is only a part of this process and offers an index to the progress of genital maturation.

results and was preferred by 2 patients because of a greater sense of well being and freedom from gastric discomfort.

Failure of spermatogenesis which is the rule in severe hypogonadism with rudimentary testes was, of course, not influenced by male hormone therapy.

Genital size and pubic-hair maturation. Definite penile growth as the result of substitution therapy was not attained in all cases. When it occurred, the first evidences appeared within a few weeks and the maximal limit was reached within 6 to 9 months. Progressive increases in the length and diameter of the organ were manifest both in the relaxed and erectile state, with all measurements augmenting concomitantly. In cases in which the pubic hair growth was absent, or deficient (with the exception of *cases* 8, 9), thickening was produced to full density and its progress charted roughly in quantitative terms. Maximal results were attained within 6 months to 2 years.

The appearance of axillary, chest and facial hirsutism in succession was delayed, the occurrence of each phase depending on the fulfillment of the previous stage. Throughout the total period of observation stimulation of the growth of face and chest hair was the least satisfactory of all and inadequate at its best. Local application of testosterone propionate inunction to these areas did not prove effective.

Deepening of the voice was satisfactory and developed in the latter stages of pubic-hair thickening and afterwards.

An enlargement of the scrotum and corrugation of the scrotal skin irrespective of the testicular mass occurred early in the course of treatment, as did prostatic enlargement to a maximal point which was less than the average development for a normal male. During the first few weeks of treatment the soft and rudimentary testes became larger, congested, more firm and defined to palpation; later they regressed to their initial state.

Analysis of the clinical findings prior to treatment with emphasis on the distinction between genital size and pubic-hair maturation has made it possible to establish criteria of prognosis for the results of treatment. The extent or rapidity of the penile growth produced was not influenced by its initial size, nor by that of the testes, nor by excessive medication, the age of the individual or the number of years he had been genitally retarded. Nor was it apparently affected by any configuration factors of fat distribution or skeletal proportions.

Presence or absence of pubic hair and the rapidity of its thickening appeared to be the sole reliable determining factor for the prediction of penile growth. Penile growth could be elicited only when evidences of public maturation[2] were not present or were incomplete. The penis had reached its maximal length at the half-way stage of pubic-hair thickening (2+). Penile growth was terminated or precluded at the time of full pubic hair density (+4).

The rapidity of the thickening of the pubic hair varied considerably and independently of the age of the individual, the testicular mass or the intensity of treatment above physiological acequacy; in some cases it required as long as 6 months for the early evidences (1+) and in others it progressed rapidly to completion (4+) within the same interval. In a given case the speed of the process could not be accurately predicted, although it seemed somewhat more delayed in the slender and light-complexioned individual, which was probably dependent on so-called constitutional and hereditary factors.

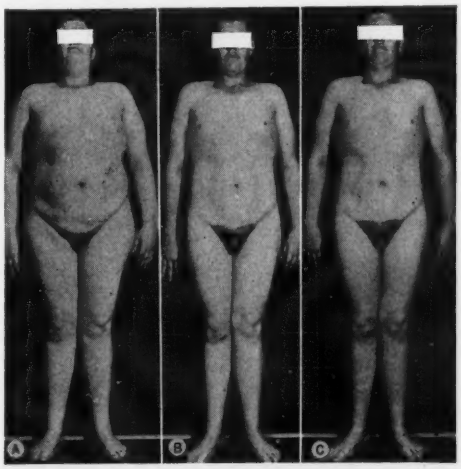

Fig. 2. STIMULATION OF GENITAL GROWTH AND MATURATION IN THE HYPOGONAD G.R., age 28. A. Prior to therapy. B. Eight months after initiation of treatment with androgens. C. Fifteen months after initiation of treatment. Maximal genital growth attained prior to development of full thickness of the pubic hair.

Effects on skin and body configuration. The skin of the untreated hypogonad individual was dry, poor in elasticity and luster. Substitution therapy, which promotes mineral and water storage, led to a marked improvement in tissue tone, with increased firmness to palpation, and surface sheen to inspection. There was a lightening of the grayish caste to the skin, particularly noted over areas poor in subcutaneous fat, as under the eyes. An increased surface moisture and oiliness became evident, with the latter particularly marked through the period of growth of pubic hair and at times becoming sufficiently severe to be associated with seborrhea and acne.

The adult hypogonad male, in agreement with

accepted clinical impressions, was of average or better height. With or without treatment, closure of the epiphyses was delayed but eventually took place long after, and only if some evidences of pubic-hair maturation had occurred. Male hormone therapy in these cases produced an undeniable acceleration of growth, both in height and in breadth (shown in shoulder girdle and facial bones) only when the epiphyses were open and usually in conjunction with pubic maturation, namely, during or immediately after thickening of the pubic hair.

More often than not the hypogonad patient appeared to be stout or obese with accumulations of fat over the chest, abdomen and hips, to an increasing degree with age. Although a feminine type of fat distribution, including mammary prominence (adipose or glandular), was not infrequent and may even be pronounced in normal individuals, it appeared to be more prevalent in the older obese type of hypogonad male. Improvement in body configuration resulted through weight loss on low-calorie diets. Improvement could also be induced, in spite of weight gain, with male hormone stimulation if further muscle development and skeletal growth could occur, usually in conjunction with thickening of the pubic hair. Marked improvements in configuration appeared in the initially lean hypogonad person, in whom pubic maturation was produced with the male hormone when the additive anabolic effects of hydration, fat, muscle and bone storage resulted in striking body changes and weight gain. Initially, as well as following treatment, the somatic pattern at its best remained at all times within the framework of hereditary trends which appeared to be of a paramount significance.

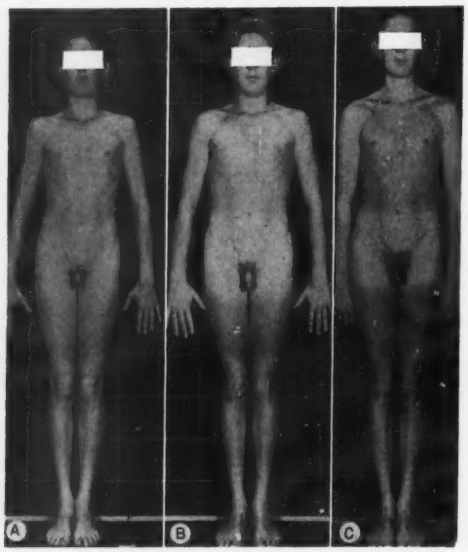

Fig. 3. Stimulation of genital growth and maturation in the hypogonad *J.H.*, age 18. *A.* Prior to therapy. *B.* Six months after initiation of treatment with androgens. *C.* Eighteen months after initiation of treatment. Maximal genital growth attained prior to development of full thickness of pubic hair.

Personality. The personality of the adult hypogonad was masculine in a sense that his interests and activities were masculine. There were no evidences of homosexual trends or the feminine type of behavior. Curiosities were directed toward the opposite sex but the contacts were avoided because of the feebleness of sex impulse and feeling of inadequacy. Impulse life, in general, as expressed in 'drive' was weak or poorly sustained, due to true fatigability in some cases, possibly to a specific effect of male hormone deficiency. Moreover, a knowledge of genital insufficiency projected itself into a sense of inadequacy toward the environment as a whole, undermining ego evaluation and creating a feeling of self-reference of inferiority. At times, periods of acute anxiety or depression occurred, but major psychoses have not been found. Compensatory behavior may become manifest at any stage of this process and, as in all bodily disabilities, depending on the type, character, intelligence and temperament of the individual, it may be an asset or detriment to his personality. It is a mistake, however, to blanket the behavior of the hypogonad under the expression 'compensating for inferiority.' Since intelligence, temperament and character in these individuals were not inherently abnormal, but followed constitutional and hereditary lines, the hypogonad sooner or later gained insight into the specific nature of his disability, and made a fairly satisfactory occupational and social adjustment to his environment.

Substitution therapy with male hormone increased the sex urge both in its psychic and physical aspects and led to some masturbatory activity and eventually to a cautious contact with the opposite sex. The prime concern of the patient in all cases was the development of adequate penile growth in order to pass as normal in appearance and performance. An increase in energy and sense of well being promoted optimism, stronger drive and aggressiveness in dealing with the environment. At times this response almost suggests a specific effect of the male hormone comparable to the specificity of benzedrine sulphate to produce a similar reaction. It must be taken into consideration, however, that a discovery of an antidote to the feeling of inadequacy is of sufficient psychogenic strength to produce the same result. Certain it is that the hypogonad under treatment was a much happier individual.

DISCUSSION

Unless a history of infection, damage or castration is available, the cause of testicular deficiency often is not well understood and may be ascribed to hormonal and developmental factors. Thus, a fat boy with hypogenitalism before puberty has been termed a 'hypopituitary' and promoted into a enuuch or 'eunuchoid' if the genitalia remain small as his legs grow long after puberty. Should he surmount both classifications in spite of subsequent accumulation of fat over chest and hips, he will then be advanced into a 'constitutional type,' in which he may have belonged in the beginning, provided the genital status is given a charitable interpretation by the physician. The triad of 'pituitary-eunuchoid-constitutional' has been overworked to explain the response of one patient to the pituitary-like sex hormone, that of another to the male hormone and of a third to neither substance. In many gonadal problems the determination of where constitutionality begins, functional abnormalities continue and pathological changes take over is often difficult, if not impossible, because of the over-lapping of all processes. Undeniable familial repetitions of patterns of structure and function of the body *status quo* and change is covered by the concept of constitution. Obviously, it is operable in normality, precipitation of disease and response to treatment; in any endocrine problem it includes both the variations in the peripheral tissues as well as the glands themselves.

This undoubtedly contributes to the clinical variable in hypogonadism and response to treatment. Observations during the past 5 years have demonstrated that the male may present problems of the reproductive system as highly specialized as those of the female. Endocrine aspermia, gynecomastia and penile hypoplasia have been noted as a solitary disturbance both in the normal male and in the adrenogenital type. In genital problems as a whole the distinction between genital (penile) growth, function and thickening of the pubic hair can be profitably stressed, not only to demonstrate their orderly relationships but their disassociations.

The adaptability of pubic hair thickening to a roughly quantitative evaluation in its onset and progression qualifies it for use in a specific definition of genital maturation at puberty, and as a reference point in the orientation of somatic and endocrine disturbance of early adulthood.

The hormonal causes of thickening of pubic hair are open to speculation. Association of this process with marked acceleration of growth of other tissues (penile, testicular, skeletal, muscular) suggests a multiplicity of physiologic causes ranging from the pituitary, if not the hypothalamus, down the scale. While the male hormone plays a dominant rôle in genital (penile) growth and neurovascular irritability, it probably acts in a contributory manner only in genital maturation.[2] Administration of male hormone to younger children causes increased penile growth and irritability but does not produce pubic hair growth; and, conversely, a considerable degree of thickening of pubic hair may be found in some young adults in spite of marked evidence of a male hormone deficiency. The termination of potential penile growth synchronous with the development of the full thick-

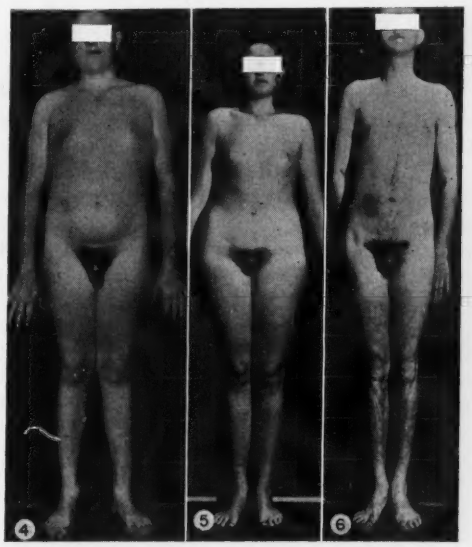

Fig. 4–6. FAILURE TO PRODUCE GENITAL GROWTH IN HYPOGONAD MALES in the presence of adequate to full thickness of the pubic hair. Period of treatment, 4 months. 4. *E.S.*, age 18. 5. *R.M.*, age 20. 6. *J.B.*, age 29.

ness of the pubic hair as observed here, actually suggests a possible antagonism in the causative factors.

Further evidence for the distinctiveness of the penile growth factor (male hormone) and that which causes genital maturation is presented by cases with marked delay in maturation progression in the presence of normal to excessive genital growth. This is demonstrated by the cases of tall boys 18 to 20 years of age who have excellent genital size but scanty pubic hair growth, and no chest and face hair (6 cases, unpublished).

In 2 cases of hypogonadism secondary to pituitary deficiency (in one case associated with a secondary Addison's disease) which have been treated with male hormone substitution therapy, favorable response in genital growth and irritability have been obtained, but not thickening of the pubic hair has occurred. The fact that there is a relationship of the

adrenal cortex to pathological hirsutism is well established. These evidences point to some cause other than the male hormone in the production of genital maturation (puberty), possibly to some 'maturity factor' in the adrenal cortex.

The distinction between genital size and genital maturation is of importance, not only in the prediction of genital growth through the action of the male hormone, but also in the exercise of greater caution in attributing other accelerated growth phenomena (skeletal) to this substance alone, when evidences of genital maturation in terms of pubic hair thickening are also progressing.

SUMMARY

1. The distinction between genital growth (penile growth) and genital maturation as revealed by pubic hair thickening is emphasized.

2. Genital growth is directly under the influence of the androgenic hormone of the testes or its exogenous substitutes. It may be produced in the absence of, as well as in the presence of partial genital maturation as gauged by thickening of the pubic hair, but it is definitely precluded by the evidences of full genital maturation in terms of pubic hair thickening. Observation of the degree of pubic hair maturation, therefore, offers a valuable clinical criterion for the prognosis of genital growth, both in the hypogonad under treatment and in the normal individual as well.

3. Genital maturation is only partly under the influence of the androgenic hormone of the testes or its exogenous substitutes. It is precipitated by this hormone only when delayed, and in the presence of an adequacy of other necessary 'maturity factors,' the nature of which is open to speculation. It is assumed that the full development of these maturity factors is responsible for the eventual termination of genital growth.

4. Methyl testosterone is a potent substitute for the androgenic hormone of the testes and stimulates genital growth and maturation when an endogenous deficiency of this substance is present and within the limits of the above-mentioned considerations. Its effectiveness in increasing the genital neurovascular irritability is more constant and depends upon the presence of an initial male hormone deficiency only. Dosage, technique of medication and side effect are discussed.

5. Testosterone propionate inunction (25 mg. per gm. of base) appears to be equally effective in maintenance of the hypogonad, requiring less of the active substance than the use of methyl testosterone orally; it is preferable in some cases because of the absence of side effects.

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Effect of Chorionic Gonadotropic Hormone and of Male Sex Hormone on Height Increase and Bone Development

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ATTENTION HAS BEEN focused in recent years on the effects of gonadotropic and sex hormones on somatic growth, especially on height and bone development. While the exact mode of action is unknown, the following may be possible factors *a*), the inherent growth-stimulating qualities which affect other somatic tissues as well as the accessory sex organs; *b*), stimulation of the growth-producing factors of the anterior pituitary gland or inhibition of the gonadotropic function of this gland with subsequent suppression of the growth function. According to Severinghaus (1) the injection of pregnancy urine preparations and of gonadal hormones have an effect on both the acidophilic and basophilic cells of the anterior lobe of the pituitary gland, although males and females do not respond similarly in all cases. The acidophilic cells, which are concerned with growth function, may also be a source of one of the two gonad-stimulating hormones of the anterior pituitary gland.

Castration of male rats in early life leads to significant inhibition of general somatic development with a resultant decrease in weight and retardation in body length as compared to normal controls. Rubinstein and co-workers (2) report that testosterone proptionate in small daily intraperitoneal injections has a stimulating effect on the growth of these castrated rats but that large doses produce a depressing effect which exceeds that of castration alone. Dosage and duration of treatment are important factors as this depression is not observed until the 24th day at which time it becomes progressively more marked.

Turner and associates (3) found that large doses of testosterone propionate given over prolonged periods of time, even when treatment was started one day after birth, did not accelerate body growth or skeletal maturation in rats, except in isolated bones. At the end of the period of observation the rate of osseous development was not increased to any greater extent than in control animals.

Clinical manifestations of the growth-stimulating effect of gonadotropin and of sex hormones are noted in both sexes at puberty in the physiological spurt of linear and general somatic growth, in addition to an increase in the size of the external and internal sex organs. Precocious puberty and increased activity of the gonads are associated with marked acceleration in both height and bone development for a short period and subsequent dwarfing occurs due to premature closure of the epiphyses. Prepubertal eunuchoidism, on the other hand, is characterized by delay in closure of the epiphyses. The resultant height depends on the functional activity of the anterior-pituitary growth hormone. Eunuchoid giantism ensues in the presence of an associated increased pituitary activity, while dwarfism occurs if the amount of growth hormone is insufficient.

Increase in height has been reported in sexually underdeveloped and underheight boys following the administration of testosterone propionate by injection (4–7), of methyl testosterone by mouth (8) and of chorionic gonadotropic hormone by injection (5, 7, 9, 10, 11).

Variable results have been reported on the effect of chorionic gonadotropin and of testosterone propionate on the excessive height of boys with eunuchoidism or other forms of milder hypogonadism. Both successful and unsuccessful curbing of height increase have been observed (5, 7).

The action of chorionic gonadotropic hormone and of testosterone propionate on osseous development and on epiphyseal closure has also been studied in association with the effects on height. McCullagh (12) originally felt that testosterone propionate did

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not affect epiphyseal development, but he now considers that, although small doses (15 to 60 mg. per week) fail to accelerate epiphyseal changes, large doses (105 mg. per week) cause a marked increase in epiphyseal age. Although the latter statement is made on the basis of observations in adult eunuchoid men in whom the epiphyses were still ununited, he warns against the use of large doses of testosterone propionate in individuals who have not as yet obtained normal adult stature, for fear of stunting of growth.

considered as instances of pseudo-cryptorchidism and are not included.

In evaluating the results in cases of cryptorchidism, a testis was considered to be completely descended when it entered into the scrotum and remained there. Descent as far as the external ring or to the upper border of the scrotum was listed as partial descent. In a few instances, the testis descended into the scrotum and then retracted, but eventually remained in the scrotum after further treatment. In these cases, the latter date was considered as that of complete descent.

TABLE 1. SUMMARY OF RESULTS IMMEDIATELY AFTER THERAPY

Case No.	Initial Age yr., mo.	Initial Height[1]	Initial Bone Age[1]	Percentage Increment in Height	Percentage Increment in Bone Age	Height at End of Treatment[1]	Bone Age at End of Treatment[1]	Treatment: Duration, mo.	Treatment: Total Dosage R.U.; mg.		Diagnosis
Group 1, receiving chorionic gonadotropin; R.U.											
4	9-0	+	N	−35	+25	+	N	7	11,600		Cryptorchidism
5	9-6	+	N	+18	+50	+	+	11	35,600		Cryptorchidism
6	10-9	+	N	+50	+160	+	+	13	36,800		Cryptorchidism
7	14-3	+	N	+69	+30	+	N	5	20,000		Cryptorchidism
9	12-0	−	N	0	0	−	N	13	40,400		Cryptorchidism, adiposogenital dystrophy
14	11-0	+	N	+29	+12	+	N	22	60,000		Adiposogenital dystrophy
16	9-10	N	−	+11	+20	N	−	16	17,000		Adiposogenital dystrophy
17	10-0	+	N	−25	0	N	N	6	11,800		Adiposogenital dystrophy
18	11-0	+	N	0	0	+	N	13	26,000		Adiposogenital dystrophy
22	9-0	−	−	+12½	+100	−	N	5	20,000		Adiposogenital dystrophy
Group 2, receiving both chorionic gonadotropin, R.U., and testosterone propionate, mg.											
1	10-11	+	+	+38	+18	+	+	24	12,200	1,470	Eunuchoidism
3	8-4	+	−	+40	+81	+	−	18	19,000	250	Cryptorchidism
10	9-6	+	N	+5	0	+	N	32	95,000	225	Adiposogenital dystrophy
11	10-2	+	+	+50	+50	+	+	11	18,000	290	Adiposogenital dystrophy
12	15-6	−	−	+156	0	−	−	18	27,000	250	Adiposogenital dystrophy with short stature
13	14-0	+	N	+40	0	+	N	15	10,250	590	Adiposogenital dystrophy
15	10-10	+	−	−27	+33	+	N	15	13,000	350	Adiposogenital dystrophy
19	12-0	+	N	+100	+133	+	+	14	5,000	820	Adiposogenital dystrophy
21	8-0	+	−	+44	+116	+	+	36	17,500	250	Adiposogenital dystrophy
24	11-6	+	−	+33	+50	+	N	24	49,000	260	Adiposogenital dystrophy

[1] Plus and minus signs indicate a height and bone age above or below the normal for that age; N, normal for the age.

Others state that moderate amounts of male sex hormones or of chorionic gonadotropic hormone do not produce progressive epiphyseal development or premature epiphyseal closure (6, 14–19).

The present report is concerned with the effects of chorionic gonadotropic hormone, with or without testosterone propionate, on the height and bone development of 20 boys who were treated for cryptorchidism and hypogenitalism.

The results on the descent of the testes and the growth of the external genitalia are discussed in a separate communication (20). All cases of cryptorchidism in this series are of the true type. Testes of the receding type, or those which could be forced into the scrotum by either manipulation or heat are

The conditions present in these boys consisted of adiposogenital dystrophy, 11 instances; eunuchoid type of adiposogenital dystrophy, 2; primary hypogonadism with giantism, 1; and cryptorchidism, 15 cases. The ages ranged from 8 to 15½ years. Fifteen were below the age of 12 years and 5 were above this age.

Roentgenograms were made of the skull and sella turcica and of the wrists at the initiation of treatment, and of the wrists at varying intervals. The bone development was measured by a modification of Todd's Standards (21), and the height by the Baldwin-Wood Standards for the medium average (22).

Treatment was given for periods ranging from 5 to 36 months and was continuous for the first 3 months and interrupted thereafter, especially during the summer months. One group of 10 boys received intramuscular injections of chorionic gonadotropic hormone[1] in doses of 250 to 500 rat or international units twice a week, with an average of 28,380 units. The second group of 10 boys had been treated with chorionic gonadotropic hormone but had not responded favorably with either the descent of the testes or the growth of the external genitalia. They received testosterone propionate[2] in doses of 10 to 25 mg. twice a week. This therapy was continued for 4 to 8 weeks and was then discontinued to be replaced by chorionic gonadotropic hormone for 1 to 3 months. This alternation was adhered to throughout the entire course of treatment except for intervals lasting from several weeks to several months, especially during the summer. In a few instances, only testosterone propionate was administered after the initial 3-month period of treatment with gonadotropic hormone.

The total dosage of chorionic gonadotropic hormone in this group ranged from 5000 to 95,000 rat or international units, with an average of 26,595; that of testosterone propionate ranged from 225 to 1470 mg. with an average of 475.5 mg. The average dosage of chorionic gonadotropic hormone for both groups was 27,487 units.

RESULTS

Height. There was an increase in height in every boy. This increase was above the normal expectancy in 14 cases, normal in 3 and below normal in 3. The average gain in height for the entire series was 32.2 per cent above the normal increment. In the 10 boys treated with chorionic gonadotropic hormone the average increase in height was 12.9 per cent above the normal increment; 6 of these showed a gain ranging from 11 to 69 per cent above the normal, 2 grew at a normal rate and 2 increased in height at a rate lower than the normal.

Better results were obtained with the boys who received the combined treatment of chorionic gonadotropic hormone and testosterone propionate, as shown by an average of 47.9 per cent increase above the normal increment; 8 of these boys showed a gain in height ranging from 33 to 156 per cent above the normal rate, one showed a slight increase above the normal and one a lower rate than normal.

TABLE 2. EFFECT OF TREATMENT ON HEIGHT

Case No.	Chronological Age: Initially yr., mo.	Chronological Age: End of treatment yr., mo.	Height, inches: Initially	Height, inches: End of treatment	Normal Height for Same Ages, in.		Increment, in., Above and Below Normal	Percentage Increment Above and Below Normal
Group 1, Chorionic gonadotropin								
4	9-0	11-0	56	58 5/8	52	56	−1.4	−35
5	9-6	11-6	56 3/4	61 1/2	53	57	+0.75	+18
6	10-9	12-6	62 1/4	67 1/2	55 3/4	59	+1.62	+50
7	14-3	15-0	65 3/8	68 3/4	63 1/2	65 1/2	+1.38	+69
9	12-0	13-3	52	54 3/4	58	60 3/4	N	0
14	11-0	13-8	60	67 3/4	56	62	+1.75	+29
16	9-10	12-3	53 1/4	58 1/4	53 3/4	58 1/4	+0.5	+11
17	10-0	11-6	54 1/4	57	54	57	−0.75	−25
18	11-0	12-0	58	60	56	58	N	0
22	9-0	11-0	49	53 1/2	52	56	+0.50	+12 1/2
Group 2, Chorionic gonadotropin and testosterone propionate								
1	10-11	13-4	67	74 1/2	56	61 1/4	+3.0	+38
3	8-4	9-6	51	55 1/4	50	53	+1.25	+40
10	9-6	14-0	54	64 1/2	53	63	+0.5	+5
11	10-2	11-2	58	61	54 1/2	56 1/2	+1.0	+50
12	15-6	17-0	60 3/4	65 7/8	66	68	+3.12	+156
13	14-0	15-3	65	68 1/2	63	65 1/2	+1.0	+40
15	10-10	14-0	59 3/4	65 1/2	55 1/2	63	−1.75	−27
19	12-0	13-2	60 1/2	65	58	60 1/4	+2.25	+100
21	8-0	11-0	53	61 5/8	50	56	+2.12	+44
24	11-6	13-6	58 1/4	64 1/4	57	61 1/2	+1.5	+33

[1] The chorionic gonadotropin was supplied by *a*) Roche-Organon, Inc., Nutley, N. J., (Pregnyl); *b*) E. R. Squibb & Sons, New Brunswick, N. J., (Follutein); and c) Ayerst, McKenna & Harrison, Rouses Point, N. Y., (A.P.L.).

[2] The testosterone propionate was supplied by *a*) Roche-Organon, Inc., Nutley, N. J., (Neo-Hombreol) and *b*) The Schering Corp., Bloomfield, N. J., (Oreton).

TABLE 3. EFFECT OF TREATMENT ON OSSEOUS DEVELOPMENT

Case No.	Chronological Age		Bone Age, yr., mo.		Actual Change, yr.	Gain Above Normal, yr.	Percentage Gain Above Normal
	Initially yr., mo.	End of treatment yr., mo.	Initially	End of treatment			
Group 1, Chorionic gonadotropin							
4	9-0	11-0	8-6	11-0	2.5	+0.5	+25
5	9-6	11-6	10-0	13-0	3.0	+1.0	+50
6	10-9	12-6	10-6	15-0	4.5	+2.8	+160
7	14-3	15-0	14-3	15-3	1.0	+0.25	+30
9	12-0	13-3	12-0	13-0	1.0	N	0
14	11-0	13-8	11-0	14-0	3.0	+0.3	+12
16	9-10	12-3	8-0	11-0	3.0	+0.5	+20
17	10-0	11-6	10-0	11-6	1.5	N	0
18	11-0	12-0	11-0	12-0	1.0	N	0
22	9-0	11-0	7-0	11-0	4.0	+2.0	+100
Group 2, chorionic gonadotropin and testosterone propionate							
1	10-11	13-4	12-3	15-0	2¾	+0.4	+18
3	8-4	9-6	6-6	8-6	2	+0.9	+81
10	9-6	14-0	9-6	14-0	4½	N	0
11	10-2	11-2	11-3	12-9	1½	+0.5	+50
12	15-6	17-0	14-0	15-6	1½	N	0
13	14-0	15-3	14-0	15-3	1¼	N	0
15	10-10	14-0	9-10	14-0	4⅛	+1.0	+33
19	12-0	13-2	12-0	15-6	3½	+2.0	+133
21	8-0	11-0	6-6	13-0	6½	+3.5	+116
24	11-6	13-6	10-0	13-0	3	+1.0	+50

This greater stimulus to growth in height in the second group is evidently due to the action of testosterone propionate. Analysis of the data for this group reveals that those who received larger doses of testosterone propionate, more than 500 mg. throughout the the course of treatment, showed a gain of 59.3 per cent above the normal increase in height, while those who received less than this amount attained an average height of 43 per cent above that of normal expectancy.

Relation of original height to results. Before treatment was started, 16 boys were above the height normal for their age. The case of one boy with primary hypogonadism, who was 11 inches above the average height for his age, will be discussed in detail later; one other boy was 6.5 inches above the normal height for his age and grew at a rate of 50 per cent above the normal increment; 4 boys were between 3¾ and 4¼ inches above the average height and grew at rates varying from 35 per cent below the normal increment to 29 per cent above normal expectancy. The remainder of the boys in this group were between 1 and 3 inches above the normal average medium height. The average increase in height for this group of originally overheight boys was 29.8 per cent above the normal increment. At the termination of treatment, 15 were above the average medium height for their ages and one was normal in height.

One boy whose height was normal at the start of treatment showed an increase of 11 per cent above the normal expectancy at the termination of therapy. Three boys were 6, 3, and 5 inches, respectively, below the average height before treatment and grew at a rate of normal, slightly above the normal and 156 per cent above the normal increment, respectively, but all 3 were still below the average medium height for their age at the termination of treatment. The average increase in height for this group was 56.2 per cent above the normal increment.

Bone development. The bone development before treatment was started was normal in 11 boys, advanced in 2 and retarded in 7. During the period of treatment it progressed at a normal rate in 6 boys, at an accelerated speed above the normal in 14 and in no case was it below the normal. The average increase was 43.9 per cent above the normal increment and was greater in those receiving both hormones (48.1%) than in those obtaining only chorionic gonadotropin (39.7%). In the former group, the range was from 12 to 160 per cent above the normal expectancy and in the latter, from 18 to 133 per cent. The greater stimulus to bone growth, with reference to height increase, evidently is also due to the action of testosterone propionate.

At the termination of the period of treatment, 6 boys showed an advanced bone development, 11 a normal bone age and 3 a retarded bone age. In the

original normal group 3 showed an advanced bone age and 8 a normal bone development; the average increase for this group was 39 per cent above the normal increment. Both of the boys with an initially advanced bone age showed still further acceleration at the termination of treatment but the average increase was no greater than that in the normal group (38 per cent above the normal increment). The increase in height in the originally retarded group ranged from normal to 100 per cent with an average of 53 per cent above the normal, but only 1 case showed an advanced bone age at the termination of treatment; 3 were normal and 3 were still retarded.

Relation of linear to osseous growth. On the basis of percentage increase above the normal, the response in the rate of bone development was greater than that of height, on the average, but not in individual instances The increase was greater in osseous development than in height in 11 instances, less in 6 and approximately the same in 3.

There is no constant relationship between the effect of treatment on height as compared to that on bone development. Both boys whose bone development was advanced before treatment showed an advance both in bone age and height above the normal at the end of the period of treatment. Those who were normal in bone development showed an ultimate advance in height in 9 instances, and in bone age in 3 instances. In the group with retarded bone development, 4 attained overheight and only one an accelerated bone development. This lack of correlation is also evident when the cases are considered from the viewpoint of height. Of the 16 boys who were overheight before treatment, 15 were overheight at the end, but only 6 showed an ultimate advance above the normal in bone age. On the basis of percentage increase, apparently the greatest advance in bone age occurred in those who were overheight and the greatest increase in height took place in those who were originally advanced in bone age. The next greatest increase is noted in those who were retarded either in bone development or height at the beginning

TABLE 4. FOLLOW-UP OBSERVATION AFTER TREATMENT WAS DISCONTINUED

	Height				Osseous Development			
Case No.	Chronological Age, yr., mo.	Height, in.	Increment Above and Below Normal	% Increment Above and Below Normal	Bone Age, yr., mo.	Actual Change, yr.	Gain or Loss Above and Below Normal	% Gain or Loss Above and Below Normal
			Group 1, chorionic gonadotropin					
4	14-0	65⅝	−0.5	−3%	14-0	3	N	0
5	12-11 14-2	64¼ 67¾	N N	0 0	14-0	1	N	0
6	13-6 14-9	70⅝ 72½	+1.1 −1.5	+44 −45	16-0 17-0	1 1	N N	0 0
7	15-6 16-10	69 70	−0.25 −0.8	−50 −44	16-0 17-0	.75 1	+0.25 −0.3	+50 −21
16	14-4	63⅝	N	0	13-6	2.5	+0.5	+25
17	12-6	59¾	+0.75	+37.5	13-0	1.5	+0.5	+50
18	13-1 13-8	63¼ 65½	+1.0 +0.37	+50 +18	13-6 14-0	1.5 .5	+0.4 N	+36 0
			Group 2, chorionic gonadotropin and testosterone propionate					
1	14-10 15-6	78 78½	−1.9 −0.2	−34 −28	16-6 17-0	1.5 .5	+0.4 N	+36 0
3	10-6	57¾	−0.3	−10	9-6	1	N	0
10	14-10 17-0	65⅝ 68½	−0.7 −0.3	−38 − 9	15-0 17-0	1 2	+0.2 N	+25 0
11	13-2	62⅝	−1.37	−45	14-0	1.25	−0.75	−38
15	14-6	66⅞	+0.3	+30	15-3	1.25	+0.75	+150

TABLE 5. RELATIONSHIP OF INITIAL BONE DEVELOPMENT AND HEIGHT

At Beginning of Treatment		At Termination of Treatment							
		Bone Development			Average percentage increase above normal	Height			Average percentage increase above normal
Bone development	No. cases	Advanced	Normal	Retarded		Advanced	Normal	Retarded	
		Number of Cases				Number of Cases			
Advanced	2	2	0	0	38	2	0	0	44.0
Normal	11	3	8	0	39	9	1	1	22.8
Retarded	7	1	3	3	53	4	1	2	38.5
Height									
Advanced	16	6	9	1	47.4	15	1	0	29.8
Normal	1	0	0	1	20.0	0	1	0	11.0
Retarded	3	0	2	1	33.0	0	0	3	56.0

of treatment. This would indicate that a greater stimulation is exerted on those already advanced and those retarded than on the normal in either bone development or height.

Age at beginning of treatment. The age at which treatment was instituted had an effect on both the height and bone development. Better results were obtained in height increase in boys above 12 years of age than in those below this age, in spite of the shorter duration of treatment and greater amount of chorionic gonadotropic hormone administered. The dosage of male sex hormone was slightly larger. The results can be explained on the basis of the added stimulation of the puberty spurt and they confirm the observations of others (11).

The percentage of increase in bone development was above the normal in both age groups, but it was less in boys above 12 years of age than in those below this age. The administration of both hormones had a greater effect on height and on bone development, irrespective of age, than that of chorionic gonadotropin alone.

Duration of treatment. The average duration of treatment was 16.2 months for the series; 11.8 months for the group which received chorionic gonadotropic hormone and 20.7 months for the boys who obtained testosterone propionate in addition.

In analyzing the results with reference to the duration of treatment, it was decided to exclude the cases of the 3 boys who received large doses of testosterone propionate, as these amounts are not usually given to boys of this age. The average figures for the remaining 17 patients show a height increase above the normal increment of 17 per cent in those treated less than 12 months and of 31 per cent for those treated more than 12 months. There is an increasing percentage above the normal increment from 6 months to 2 years of treatment but not beyond this period. The results obtained in short periods of treatment are not constant, for in the 3 patients who were treated for 5 to 7 months, the increase in height was *a*) normal, *b*) 35 per cent below the normal increment and *c*) 69 per cent above that of normal expectancy, respectively.

The rate of bone development likewise was affected by the duration of treatment, as evidenced by an average of 38 per cent increase above the normal increment in cases treated less than 12 months and of 46 per cent increase above the normal increment in those treated more than 12 months.

Dosage. The effects of the dosage of chorionic gonadotropic hormone were analyzed in 17 patients who received this hormone alone or in alternation with testosterone propionate in dosages as high as 500 mg. There was an average height increase above the normal increment of 15 per cent in those boys who received less than 20,000 I.U. or R.U., and of 36 per cent in those who received 20,000 or more units. The results in bone development are not consistent with those on height, as the lower dosage was associated with a greater rate of development (51 per cent above the normal increment) than was the case with

TABLE 6. RELATIONSHIP BETWEEN EFFECT OF TREATMENT ON CRYPTORCHIDISM AND HYPOGENITALISM AND ON INCREASE IN HEIGHT AND BONE DEVELOPMENT

No. of Cases	Results	Average Percentage Height Increase Above Normal Increment	Average Percentage Increase in Bone Development Above Normal Increment
	Cryptorchidism		
6	Complete descent	19.5	51.0
6	Partial descent	26.6	49.5
3	No effect	14.0	62.0
	Hypogenitalism		
9	Marked effect	34.0	47.0
11	Moderate or slight effect	28.0	42.0

larger amounts (34 per cent above that of normal expectancy).

Cryptorchidism and hypogenitalism. The results of treatment in the 15 instances of cryptorchidism were *a*) the production of complete descent in 6 cases, *b*) partial in 6 and *c*), failure in 3. There was no correlation between the increase in body height and the descent of the testes as *a*) the greatest statural increase occurred in the boys in whom there was partial descent, *b*) less in those with complete descent and *c*), least in those with failure of descent. The difference in the height increase between the cases with complete descent and those which were failures was only 5.5 per cent.

There was, also, no correlation between the advance in bone age and the effects on cryptorchidism since the greatest degree of growth acceleration occurred in those boys in whom there was failure of descent; there was less in those with partial descent and the least acceleration occurred in those with complete descent. This lack of correlation is exemplified in a boy of 8 years of age who, at the beginning of the period of treatment presented a picture of pronounced adiposogenital dystrophy with infantile genitalia and bilateral abdominal cryptorchidism (*case 21*). He was above the average height for his age but was retarded 18 months in bone development. Intermittent treatment with both chorionic gonadotropic hormone and testosterone propionate, thyroid substance by mouth and diet over a period of 3 years resulted in a loss of weight, an increase of 44 per cent above the normal increment in height and an advance of 116 per cent increase above the normal expectancy in bone development. The sesamoid bone appeared and the general bone picture was that of a boy at puberty of about 13 years. The external genitalia did not show a commensurate growth, the penis was that of a 10-year-old boy, the scrotum was small, pubic hair was present but the testes were still in the abdomen. This case illustrates the possibility of producing premature appearance of the bone development of puberty without, however, *a*) stunting the growth, *b*) affecting the descent of the testes, or *c*) producing closure of the epiphyses.

There was apparently no correlation between the effect on genital development and that on statural and bone growth. There was a slightly greater average increase in both height and bone age in those boys who showed effects of marked stimulation of the gonads than in those with moderate or slight effects, but the differences were too small to be of any significance. There are marked variations between individual cases in each group.

The results in primary hypogonadism are exemplified in the case report.

TABLE 7. RELATIONSHIP OF AGE AT INITIATION OF TREATMENT TO RESULTS OBTAINED

Age	Number of Cases	Duration of Treatment	Average Amount of Hormones Given	Percentage Increase in Height Above Normal Increment			Percentage Increase in Bone Age Above Normal Increment		
				With chorionic gonadotropin	Chorionic gonadotropin and testos. prop.	For series	Chorionic gonadotropin	Chorionic gonadotropin and testos. prop.	For series
Below 12 yr. of age	15	17.3 mo.	29,966 R.U. or I.U. of chorionic gonadotropin 206 mg. testosterone propionate	21.6	31.4	36.2	45.2	49.7	47.7
Above 12 yr. of age	5	13 mo.	18,450 R.U. or I.U. of chorionic gonadotropin 332 mg. testosterone propionate	34.5	98.6	73	15.0	44.3	32.6

CASE REPORT

L.E., when first seen at the age of 10 years and 10 months, presented a tall and thin appearance, an almost infantile penis and small testes in an underdeveloped scrotum. His height was 67 inches, upper longitudinal measurement 31 in., lower longitudinal measurement 36 in., and span, 69 inches. He had never received endocrine therapy. He gave a history of having grown 9 inches in the previous 3 years, which was equivalent to 50 per cent increase above the normal increment for that period. He was given chorionic gonadotropic hormone parenterally in doses of 250 to 500 R.U. for 8 months and then testosterone propionate for the next 20 months. Treatment was discontinued when he was 13 years and 4 months old because of marked enlargement of the penis and testes,

and the appearance of secondary sex characteristics. He was 74¼ inches tall at the latter time, an increase of 7¼ inches, equivalent to a percentage increase of 38 per cent above the normal increment. After the cessation of treatment, the height increased at approximately the same rate of speed for the next 16 months and then slowed down to a normal rate during the following 6 months. He was 78½ inches tall at 15½ years.

The bone age was 1 year and 5 months, or 13 per cent, advanced above the normal bone age before treatment. After 28 months of therapy the bone development advanced 33 months, at a rate of 18 per cent above the normal increase. There was a spurt for 16 months after treatment was discontinued which was equivalent to an increase of 36 per cent above the normal increment; this was followed by a slowing down to a normal rate for the remainder of the period of observation. At 15½ years of age he had a bone age characteristic of 17 years.

Follow-up observations were made on 12 boys for periods varying from 6 months to 3 years after treatment was discontinued. All but one were 12 years of age or older at the time and subject to the same physiological spurt of growth of puberty. Growth continued in all, but at 3 different tempos: *a*), the rate was reduced in 7 boys who had shown an increase above the normal increment during treatment and in one boy who had had a diminished rate of growth; *b*), the rate was accelerated in 2 boys who had a normal growth increase and in 2 who had shown a lower-than-normal increment during treatment; and *c*), the rate was further reduced in one of the boys in the first group and in one of the boys in the second group after an initial acceleration.

These figures imply that in the majority of cases there is growth stimulation for the duration of treatment only, but that in a small percentage of cases growth may persist after treatment is discontinued. The accelerated rate may later be followed by a slowing down in growth.

The same tendencies were noted in bone development as evidenced by a decreased rate in 6 cases, an accelerated speed in 5 and no change in the growth tempo in one case; there was a subsequent diminished rate in 3 of the accelerated growth group. The rate of bone development eventually dropped from a height of 18 to 160 per cent above the normal increment to the normal or below the normal in 8 cases; it remained at about the same rate in 2 and was increased in 2. In one of the latter cases (*case 15*) an increase of 33 per cent above the normal increment during treatment was followed by an acceleration of 150 per cent above that of normal expectancy after treatment was discontinued. There was also a marked increase in height after treatment was stopped.

SUMMARY AND CONCLUSIONS

The effects of chorionic gonadotropic hormone and testosterone propionate on the height and bone development were studied in 20 boys suffering from hypogonadism, hypogenitalism and cryptorchidism. The ages ranged from 8 to 15½ years with 15 boys below the age of 12 years and 5 above this age. The duration of treatment varied from 5 to 36 months.

The patients are divided into two groups: *a*), those who received chorionic gonadotropic hormone and *b*), those receiving chorionic gonadotropic hormone alternating with testosterone propionate. The average dosage for the first group was 28,380 R.U. or I.U. of chorionic gonadotropin and for the second group, 26,595 R.U. or I.U. of chorionic gonadotropic hormone and 475 mg. of testosterone propionate.

Every boy increased in height while under treatment, but in 3 different tempos: Fourteen grew at a rate greater than normal, 3 at the normal rate and 3 at a rate slower than normal. The average gain for the entire series was 32.2 per cent above the normal increment; it was greater in those receiving both hormones (47.9 per cent above the normal increment) than in those who obtained chorionic gonadotropic hormone alone (12.9 per cent above the normal increment). In the former group a greater increase in height was observed in those who received larger amounts of testosterone propionate.

The original heigth apparently had an influence on the results. Better results were obtained on the average, in those who were shorter than normal for their age at the beginning of treatment (56.2 per cent above the normal increment) than in those who were taller than normal (29.8 per cent increase above normal expectancy) or normal in height at the time treatment was begun (11 per cent increase above the normal rate). In spite of this increased rate of growth, the 3 boys who originally were retarded in growth at the beginning of treatment were still shorter than normal at the termination of treatment. In the group of boys originally taller than normal one was of normal height and all of the others were above after therapy. There was a slight increase in height in the boy who was of normal height at the time treatment was initiated.

The bone development progressed at a normal rate in 6 boys, at an accelerated rate in 14 and in no case was it below the normal. The average increase was 43.9 per cent above the normal increment for the series, 48.1 per cent for those boys who received both hormones and 39.7 per cent above the normal expectancy for those who received chorionic gonadotropic hormone alone. Here also, better results were obtained in patients with an initially retarded bone development (53 per cent above the normal increment) than in those with an originally normal (39 per cent increase above the normal) or an initially advanced bone age (38 per cent above the normal increment). At the termination of treatment, 1 case in the

originally retarded group showed an advanced bone age, 3 had a normal bone age and 3 were still retarded. In those with an initially normal bone age, 3 were advanced and 8 were normal. The 2 boys with advanced bone development at the start of treatment showed a still further advance at the termination of treatment.

The response in bone development was greater than that in height increase, but there was no constant relationship in the effect of treatments. On the basis of percentage increase, apparently, the greatest advance in bone age occurred in those individuals who were taller than normal and the greatest increase in height took place in those who were originally advanced in bone age. The next greatest increase is noted in those who were retarded in either bone development or height at the beginning of treatment. This would indicate that a greater stimulation is exerted in those individuals who are already advanced and in those who are retarded than in the individuals who are normal in either bone development or in height for their age.

The age at which treatment is instituted has an effect on the response in both height and bone development. Better results were obtained in height increase in boys above 12 years of age than in those below this age. This may be explained on the basis of added stimulation to the puberty spurt. The increase in bone development, however, was greater in those below 12 years than in those above this age.

Duration of treatment has an effect on the result in both height and bone age. There is an increasing percentage increase above the normal increment as the result of treatment for 6 months to 2 years, but not beyond this period. The results for shorter periods are not consistent.

There seems to be a relationship between the dosage and the effect on height, but not between dosage and the results in bone development. There is no relationship between the increase in height or the advance in bone development and the effect on the cryptorchidism and hypogenitalism. It is possible to obtain a marked acceleration in bone age without an associated stunting of growth or beneficial effect on cryptorchidism.

Administration of large doses of chorionic gonadotropic hormone and of testosterone propionate to a boy of 11 years of age with eunuchoidism resulted in a slowing down of an increased rate of linear growth, but there was no cessation of height increase. There was also an acceleration of bone development, but no closure of the epiphyses. Premature closure of the epiphyses was not observed in any boy in this series.

Follow-up observations on 12 boys showed that in the majority of cases the stimulative effect of chorionic gonadotropic hormone and of testosterone propionate on both height and bone development is present for the duration of treatment only, but that in a small percentage of cases accelerated growth may persist after the termination of treatment. This may be followed later by a slowing down in the rate of both height and bone growth.

We conclude that chorionic gonadotropic hormone and testosterone propionate have stimulating effects on height and bone development in prepubertal and adolescent boys. When both are given in successive courses of treatment they have a greater effect than chorionic gonadotropin alone; this is probably due to the action of testosterone propionate. In the dosages used in this series (250 to 500 R.U. or I.U. of chorionic gonadotropic hormones and 10 to 25 mg. of testosterone propionate, over extended periods of time), there was not a single instance of premature closure of the epiphyses, or of stunting of growth. Both hormones, either alone or in combination, are valuable agents in the treatment of pre-adolescent short stature.

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Urinary 17-Ketosteroid Assays in Clinical Medicine[1]

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THE PRESENT COMMUNICATION surveys the practical usefulness of 17-ketosteroid assays in clinical medicine. In adhering strictly to this subject, many of the interesting and fundamentally important observations on the chemistry and physiology of the urinary 17-ketosteroids are not discussed. However, references to papers which give this type of information are given whenever possible.

METHODS OF ASSAY

Because the usefulness of any laboratory determination depends upon its accuracy and availability a word concerning each of these aspects of assay is pertinent to our subject. Reliable evidence indicates that there are interfering chromogens in urine which, when present in large quantities, may give rise to errors in the commonly used colorimetric assay (Zimmerman reaction). Unless steps are taken to eliminate these errors, they lead to an overestimation of the 17-ketosteroid content. Fortunately, simple procedures for detecting the presence of and for eliminating most of the errors due to these interfering substances have provided reasonably reliable methods of determining the total 17-ketosteroid content of the urine (1–4).[2] In addition, procedures suitable for use in hospital laboratories are available for separating the total 17-ketosteroid of a single 24-hour urine specimen into alpha-alcoholic, beta-alcoholic and non-alcoholic fractions (5, 6).

GENERAL SIGNIFICANCE

The evidence of today suggests that the urinary neutral 17-ketosteroids are excretory transformation products of certain adrenal cortical steroid hormones, and to a lesser extent of testicular steroid hormones (3, 7). Thus the 17-ketosteroid output may be considered to be proportional to, or a rough index of, the secretory activities of these two endocrine glands. However, because the secretory activities of the adrenal cortex and testes are influenced by anterior pituitary and thyroid hormones, the 17-ketosteroid assay may also give indirect information concerning their secretory activities. Thus, hypopituitarism and hypothyroidism, as well as hypofunction of the adrenals, may result in a marked lowering of the 17-ketosteroid output. Testicular deficiency results in a moderate decrease in output. On the other hand, hyperpituitarism and hyperthyroidism do not cause a significant elevation in 17-ketosteroid excretion. Indeed, in most instances abnormally high rates of excretion are associated with changes in adrenal cortical function or the presence of a testicular tumor. Theoretically, therefore, assay of urinary 17-ketosteroids excretion should provide information concerning certain aspects of adrenal, testicular, pituitary and thyroid function.

NORMAL TOTAL URINARY 17-KESTOSTEROID EXCRETION

Before the urinary excretion of 17-ketosteroids can be used as an index of either normal or abnormal endocrine function, normal standards of excretion, including the daily fluctuation, had to be established. Studies of the output of total 17-ketosteroids by normal individuals during consecutive 24-hour periods of time have shown that the output is not absolutely constant from day to day (8, 9, 10). However, the fluctuations which occur under normal circumstances are not great, the chances being two to one that a single assay will fall within 15 per cent of the 17-ketosteroid value obtained by averaging 30 or 40 consecutive daily assays. The normal fluctuations have not been explained and do not appear to bear any systematic relation to such phenomena as the menstrual cycle. It therefore appears that one or two *accurately timed and collected* 12-hour or 24-hour specimens of urine suffice for assays for most clinical diagnostic purposes.

[1] Such data of this paper as originated in this department are from studies aided by a grant from the Commonwealth Fund of New York.

[2] There is an error on page 211 of the paper listed as reference 4. On the second and third lines from the bottom of the page $E_g:E_b$ should read $E_b:E_g$.

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In the left-hand section of figure 1 representative measurements of the 17-ketosteroid excretion by normal children are plotted as the ordinate against their age as the abscissa. Values of 17-ketosteroids for adult women and men, respectively, are presented in the middle and right-hand sections of the same figure. Average 17-ketosteroid values are represented by circles. The ranges in values are indicated by vertical lines running through the circles. The data are expressed in milligrams per 24 hours after applying corrections to eliminate over-estimation due to interfering urinary chromogens. Numerical references to the sources of these data are included at the top of the figure.

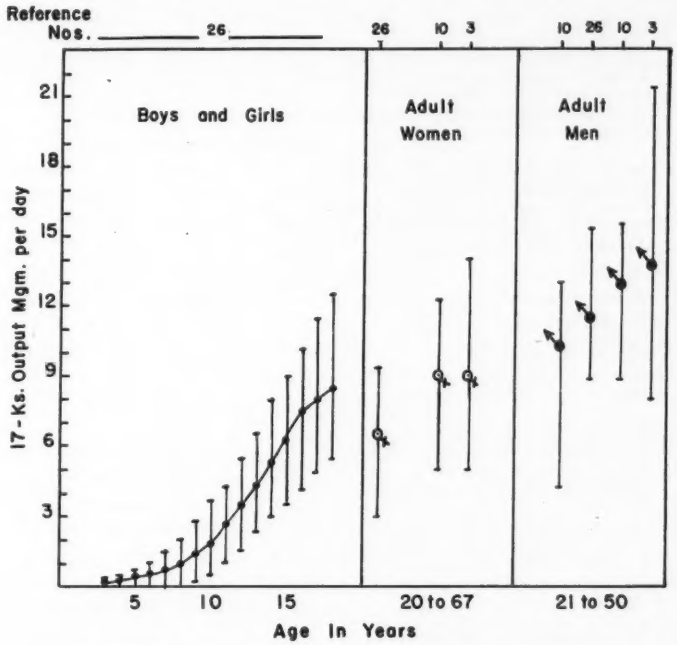

Fig. 1. 17-KETOSTEROID EXCRETION BY NORMAL SUBJECTS OF VARIOUS AGES

The solid curve running upwards from left to right through the average values for children shows that boys and girls excrete essentially no 17-ketosteroids from the time they are born until they are 7 or 8 years old. From then until they reach approximately 18 years of age the 17-ketosteroid excretion gradually increases to adult levels.

The average values for boys and girls of the same age are approximately equal. Men, however, have a higher average 17-ketosteroid output than women. It is not yet known at what age this sex difference becomes evident. The sex difference is not as clean-cut as the age effect, since the highest values found for normal women are higher than the lowest values for normal men. The higher values in men may be explained by the fact that the testes contribute to the 17-ketosteroid output, whereas the ovaries of the women do not. It is also possible that this sex effect is due largely to differences in the adrenal cortical activity of men and women.

Although such measurements as are available on aged subjects are not directly comparable to those of figure 1, they suggest that the average 17-ketosteroid output falls during senescence (11, 12, 13).

TOTAL URINARY 17-KETOSTEROID EXCRETION IN ABNORMAL CONDITIONS

The establishment of preliminary normal standards of reference for individuals of varying ages and of the dependability of one or two determinations permits tentative appraisal of the urinary 17-ketosteroid excretion in various conditions in terms of normal, decreased or increased excretion. Table 1, lists according to the presenting symptom and sex of the patient, conditions in which 17-ketosteroid assays are of diagnostic value, together with the 17-ketosteroid excretion values found in each condition. There follows in the text a brief discussion presented according to the presenting symptom as given in the table. Numerical values have not been used for recording the 17-ketosteroid output because all of the values

reported in the literature are not directly comparable and because the normal 17-ketosteroid excretion is variable. Instead, plus and minus signs indicate whether the designated excretion tends to be abnormally high or low. A key to the significance of these signs is appended to the table.

Precocious or Abnormal Masculinization (Virilism)

This heading includes boys with masculine sexual precocity and women and girls with virilism. Experience has shown that it is often difficult to locate the exact cause of the complaint by history and physical

TABLE 1. 17-KETOSTEROID EXCRETION IN SELECTED CONDITIONS

Presenting Symptom	Causes (References are given in parentheses)	Sex	Total 17-Ketosteroid Excretion[1]	Beta-alcoholic and Non-alcoholic 17-Ketosteroid Excretion[1]
A Precocious or abnormal masculinization (Virilism)	1. Adrenal cortical carcinoma (3, 6, 7, 19 to 24)	♂ and ♀	+++	+++
	2. Adrenal cortical hyperplasia (3, 22, 23, 24)	♂ and ♀	++ to +++	o to +
	3. Testicular interstitial cell tumor. (25) (one case)	♂	+++	?
	4. Central nervous system lesion (26)			
	Physiologic accelerated adolescence (26, 27)	♂	+	o
	5. Ovarian arrhenoblastoma (3, 28)	♀	o	o
B Precocious or abnormal feminization (Gynecomastia)	1. Adrenal cortical carcinoma (29) (one case)	♂	?+++	+++
	2. Ovarian granulosal cell tumor (30)	♀	o	
	3. Central nervous system lesion (3, 26, 28)			
	Physiologic accelerated adolescence (3, 26, 27, 28)	♀	+	o
	4. Associated skin pigmentation and bone cysts. (3) (one case)	♀	o	
C Retarded Sexual Development or Hypogonadism	1. Hypopituitarism (3, 16, 26, 31,)	♂ and ♀	≡	
	2. Hypothyroidism (3, 26)	♂ and ♀	≡	
	3. Castration			
	Primary gonadal deficiency	♂	o to =	
	(3, 7, 13, 17, 32–35)	♀	o to −	
	4. Debility, malnutrition (3, 11, 16)	♂ and ♀	o to =	
D Dwarfism	1. Hypopituitarism (3, 16, 26)	♂ and ♀	≡	
	2. Hypothyroidism (3, 16, 28)	♂ and ♀	≡	
	3. Familial or non-endocrine (28)	♂ and ♀	o to −	
	4. Associated with anovarianism (3, 17)	♀	− to =	
E Overweight	1. Cushing's disease: (3, 20, 23, 24)	♂ and ♀		
	a. with adrenal cortical carcinoma		+++	+++
	b. without adrenal cortical carcinoma		o to +	o
	2. Dietary plus constitutional factors (26) (children)	♂ and ♀	o to +	o
	3. Hypothyroidism (3)	♂ and ♀	≡	
F Fatiguability and weakness	1. Addison's Disease (3, 28, 32)	♂	− to =	
		♀	≡	
	2. Hypopituitarism (3, 16)	♂ and ♀	≡	
	3. Hypothyroidism (3, 16, 28)	♂ and ♀	≡	
	4. Malnutrition (3, 11, 12, 13, 16)	♂ and ♀	o to =	
	Anorexia nervosa			
	Chronic illness			
	Non-endocrine carcinoma			
	5. Cushing's disease (see E 1 above)			

[1] Key to symbols: N, within normal limits; −, low normal or slightly below normal limits; =, definitely below normal limits, but more than 1 mg. per day, (applies only to subjects over 12 years old); ≡, very low: usually between 0.0 and 0.5 mg. and never over 1.0 mg. per day (application restricted to subjects over 12); +, elevated to correspond to average normal for older children or adults, (applies only to children); ++, moderately high: *i.e.* more than 6 mg. at 6 years, 10 mg. at 10 years, 15 mg. at 15 years, 18 mg. for adult women or 21 mg. for adult men; +++, Very high: more than 35 mg. per day.

A review of figure 1 shows that, while it is possible to detect an hypo-excretion of 17-ketosteroids by adults and older children, it is impossible to detect abnormally low values for children under 8 or 9 years. On the other hand, abnormally high values can be recognized easily in individuals of any age.

examination. Table 1 shows that the 17-ketosteroid measurement gives information which aids in determining the cause.

Males. In the male subject, a very high *total* 17-ketosteroid value indicates that there is either adrenal cortical carcinoma, adrenal cortical hyperplasia or

testicular interstitial cell tumor. Male patients with either of the two adrenal cortical diseases usually have testes which are of normal size for their age. In rare instances there may be enlargement of the testes due to the presence of aberrant adrenal cortical tissue. Testicular interstitial-cell tumors, on the other hand, usually cause one of the testes to become abnormally enlarged. Thus, the chances are that a patient who is excreting very large quantities of 17-ketosteroids, but has normal-appearing testes, has one of the two adrenal cortical diseases. These may be distinguished readily by determining the urinary excretion of the beta-alcoholic and non-alcoholic 17-ketosteroids. The rates of excretion of both fractions are very high in adrenal cortical carcinoma but are normal or only slightly elevated in adrenal cortical hyperplasia.

Sexual precocity in males associated with normal or slightly elevated 17-ketosteroids values is believed to be due to an increase in anterior pituitary secretory activity such as occurs normally at an older age. In boys, both testes are precociously enlarged and sperm may be demonstrable in the seminal fluids or by testicular biopsy. The increased pituitary activity may be due to central nervous system lesions such as pineal tumor, hydrocephalus or tumors of the floor of the third ventricle. These lesions may be very difficult to detect clinically. Therefore, one cannot always determine whether or not this type of precocity is pathologic.

Females. In virilized women and girls, a very high 17-ketosteroid excretion means that the patient has one of the two adrenal cortical diseases, while a normal or slightly elevated 17-ketosteroid output is suggestive of ovarian arrhenoblastoma. As in the male, only adrenal cortical carcinoma is characterized by a very high beta-alcoholic and non-alcoholic, as well as total 17-ketosteroid output.

Hirsutism is one of the characteristics of virilism in females. Patients with simple hirsutism tend to have a normal level of 17-ketosteroid excretion as do subjects with ovarian arrhenoblastoma. However, in simple hirsutism the clitoris is usually of normal size, whereas it tends to be markedly enlarged when there is an arrhenoblastoma.

Precocious or Abnormal Feminization (Gynecomastia)

This title includes girls with feminine sexual precocity and men or boys with gynecomastia. The girls show mammary development, but need not be having menstrual periods. Section B of table 1 gives a partial list of causes and the corresponding 17-ketosteroid output.

It is seen that the feminization due to adrenal cortical carcinoma is characterized by a very high 17-ketosteroid excretion. In other conditions associated with gynecomastia the 17-ketosteroid output is either normal or but slightly elevated.

In precociously developed girls, a normal or slightly high 17-ketosteroid value is consistent with either ovarian granulosal cell tumor or with accelerated adolescence secondary to increased anterior pituitary activity. As was the case in boys, the increase in pituitary function apparently may be spontaneous or may be related to a lesion of the central nervous system. If a pelvic or lower abdominal tumor can be felt, the chances are that one is dealing with an ovarian tumor. If the child has evidences of central nervous system disease, it is probable that the precocity is related to it. In most instances, in the absence of either of these conditions, the child represents one extreme of the normal variations in time of onset of adolescence.

Retarded Sexual Development or Hypogonadism

Section C of table 1 shows that patients with this complaint may be divided into groups characterized respectively by *a*) a 17-ketosteroid excretion level which is very abnormally low or *b*) a 17-ketosteroid excretion value which is normal or only moderately low. Very low values are almost always due to hypopituitarism or hypothyroidism. On the other hand, moderately low or normal values indicate that the complaint is due to some other cause, such as primary gonadal deficiency or debility nor primarily of endocrine origin. When primary gonadal deficiency occurs without an associated pituitary or thyroid lack, large quantities of the gonadotropic hormones (FSH) may be demonstrable in the urine (3, 14).

Dwarfism

Retarded growth and retarded sexual development often occur together. When either of these disturbances is due to hypopituitarism or hypothyroidism, the 17-ketosteroid output tends to be very abnormally low (table 1, section D). There are usually fairly characteristic differences in the clinical appearance of patients with each of these diseases. The pituitary dwarf tends to have normal body proportions, to be mentally alert and to have smooth, fine-textured skin. Occasionally these patients have symptoms of signs of an expanding intracranial lesion. The hypothyroid dwarf, on the other hand, tends to have short extremities, to be dull mentally and to have rough, coarse-textured, cool, dry mottled skin. Measurements of the serum phosphatase and insulin sensitivity may help to distinguish between these two types of patients (15, 16). Their response to thyroid therapy also differs. While the thyroid dwarf responds satisfactorily to thyroid, the pituitary dwarf

responds poorly and may even develop symptoms of acute adrenal cortical insufficiency.[3]

A normal 17-ketosteroid excretion in a dwarfed patient essentially rules out the two foregoing diseases. Normal values have been observed in short but otherwise apparently normal children. Some of these have short siblings or parents; others are just beginning to grow rapidly.

Moderately low values have been observed in a group of moderately dwarfed girls who lack ovaries (3, 17). These girls fail to develop sexually and have a strongly positive urinary FSH test.

The 17-ketosteroid excretion in individuals whose growth and development is retarded because of congenital heart disease, chondrodystrophies, renal disease, chronic infection or malnutrition has not been studied adequately as yet.

Overweight

Section E of table 1 presents the trend in 17-ketosteroid excretion by patients who are overweight from several designated causes. In Cushing's disease, the total as well as the beta-alcoholic and non-alcoholic 17-ketosteroid output tends to be very high if the subject has an adrenal cortical carcinoma, but tends to be essentially normal if there is no adrenal cancer. Patients with this disease complain of weakness (see below) and have osteoporosis, hypertension, atrophic skin and other signs which serve to distinguish them from most other types of overweight individuals.

In addition to certain patients with Cushing's disease, patients who are obese simply because they eat too much, or because they have a 'constitutional tendency' to become fat tend to have a normal or slightly increased 17-ketosteroid output. These patients are probably not suffering from hypopituitarism, hypothyroidism or hypoadrenocorticism, because any of these diseases will cause a marked lowering of the 17-ketosteroid output. It is seen that very low 17-ketosteroid values are observed in patient who are overweight because of myxedema. The myxedema may be due to simple hypothyroidism or may be an evidence of thyroid deficiency which is secondary to anterior pituitary deficiency.

Fatigability and Weakness

The available information (table 1, section F) suggests that the 17-ketosteroid measurement is of value in distinguishing patients who complain of easy fatigability and weakness because they have a primary glandular deficiency from patients with diseases such as anorexia nervosa. Patients with Cushing's disease (see section E) have normal or high values. In chronic illnesses from any cause there is a tendency for the 17-ketosteroid output to be moderately lowered. However, with the exception of male patients with Addison's disease, all patients with marked adrenal cortical, thyroid or pituitary deficiency tend to have still lower values which in most instances approximate zero. Equally low 17-ketosteroid values have been obtained in a patient who was having steatorrhea and was deficient in all of the fat soluble vitamins (18). Very low values are also encountered occasionally in patients with severe hepatic insufficiency (3). Because these latter two diseases have striking clinical characteristics, they should not be difficult to recognize.

[3] Marked anterior pituitary deficiency results in a functional deficiency of thyroid, adrenal cortical and gonadal activity.

SUMMARY

The urinary 17-ketosteroid measurement has earned a place among those clinical laboratory procedures which provide diagnostic information. Determinations of the 17-ketosteroid output are particularly helpful in detecting hyperfunction and hypo-function of the adrenal cortex and hypo-function of the thyroid and pituitary glands.

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Clinical Reviews in Andrologic Endocrinology

III. Treatment of Seminal Failure

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In a preceding communication (1) the diagnosis and therapy of combined androgenic deficiency and seminal inadequacy were considered. However, deficiencies in seminal function are observed commonly in males who present no evidences of androgenic failure or other sexual incompetency as evaluated by present diagnostic criteria. Moreover it is unlikely that pronounced grades of hypogonadotropic failure exist in these patients for, if that were true, androgenic deficiency states would likewise be noted. The consideration of seminal inadequacy alone, therefore, assumes definite clinical importance.

Impairment of seminal function of the male, unaccompanied by androgenic failure, may be due to several factors: *a*) intrinsic testicular failure due to maldescent; *b*) extra-endocrine factors; *c*) altered metabolism due to thyroid disease; *d*) altered metabolism due to adrenal disease; *e*) inadequate gonadotropic activation of the germinal epithelium due to low-grade pituitary deficiency; and *f*) intrinsic germinal failure of the testes. Identification and evaluation of these various factors defines the therapeutic approach and, to a limited degree, determines the prognosis. The diagnosis and treatment of the first four classes of causes are relatively satisfactory; the diagnosis and therapy of the latter two classes, i.e., inadequate gonadotropic stimulation or intrinsic end-organ non-responsiveness, are unsatisfactory. In the preceding paper (1) a method for differentiating between these by therapeutic testing with gonadotropic preparations was outlined. The clinical data concerning these diverse etiologic factors will be considered briefly.

Seminal failure due to cryptorchidism

Therapy of cryptorchidism, either unilateral or bilateral, is indicated chiefly for three reasons. *a*). Inasmuch as the later stages of spermatogenesis are impaired in ectopic testes (2–8), deposition of the testes to the scrotum constitutes effective therapy of existing or anticipated sterility. *b*). Although some experimental evidence (9, 10) suggests no impairment of endocrine function of ectopic testes, most observers (11, 12) believe eventual reduction of endocrine function results from prolonged states of cryptorchidism. *c*). Recent studies (13) indicate that 11 per cent of all testicular tumors are found in retained testes, suggesting, therefore, a pertinent indication for deposition of ectopic testes to the scrotum in order to reduce trauma and to permit more satisfactory observation (14).

Prior to the onset of adolescence, there is little evidence that the histological pattern and physiology of undescended testes differs from that of scrotal testes (12); following adolescence, the undescended testes undergo progressive deterioration, the germinal function being involved first. Wangensteen (15–17) reported the non-existence of viable spermatozoa in the seminiferous tubules of undescended testes following adolescence. Weisman (12, 18) observed that sterility is a usual accompaniment of bilateral cryptorchidism. On the other hand, exhaustive surveys of the literature by Meyer (19) in 1927 and Rea (20) in 1939 revealed a number of instances in which motile spermatozoa were recovered from retained testes after adolescence and in which fertility was believed to be existent. Rawling (21) reported spermatogenic function in 10 of 27 cases of bilateral cryptorchidism. Uffreduzzi (22) observed spermatozoa in the testes of 10 per cent of his patients with cryptorchidism. Marechal, quoted by Wangensteen (15), observed the continuance of spermatogenesis in 50 instances of bilateral cryptorchidism. However, present knowledge (12) warrants the conclusion that the majority of cryptorchids is relatively sterile and that the degree of sterility advances with the number of years since adolescence.

The diagnosis of cryptorchidism includes the differentiation between migratory retraction of the testicle, known commonly as pseudocryptorchidism, and true retention. Doubtless, many enthusiastic reports concerning the efficacy of diverse therapeutic

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measures or the existence of fertile states may have concerned instances of pseudocryptorchidism. Migratory testes do not require therapy and tend to remain permanently within the scrotum following adolescence.

Hamilton and Hubert (23) and Thompson and Heckel (24) have outlined the salient features of the differentiation between migratory testes and retained testes. Briefly, the technique of examination includes these procedures: *a*) a carefully-taken history concerning scrotal development; *b*), a comprehensive knowledge of the pathologic anatomy of undescended testes; *c*), complete relaxation of the patient induced by reassurance, leisurely performed examinations; *d*), application of heat locally to those muscles in the scrotum and groin which cause retraction of the testicle; *e*), examination of the patient in the upright position; and *f*), repeated examinations on subsequent visits.

Considerable difference of opinion exists concerning the optimum time for institution of therapy, either endocrine or surgical, of cryptorchidism. Cabot (25) advocated endocrine therapy of cryptorchid patients between the ages of 3 and 7. Pleas for early therapy of cryptorchidism were advanced by Rubinstein (26), Nixon (27), Zelson (28), Sexton (29) and Thompson (30). On the other hand, Mimpriss (31) delays therapy until the age of 10 believing that spontaneous descent would have occurred prior to that age, a view shared essentially by Weisman (12).

There are three modes of therapy for cryptorchidism: *a*) expectant treatment; *b*) endocrine therapy; and *c*) surgical procedures. These will be considered briefly.

Expectant Treatment

Although it is conceded generally that in many cases retained testes will descend at adolescence, many observers (14) criticize the expectant management of cryptorchidism on the grounds that irreparable tubular damage of the ectopic testes resulting from increased thermal levels and trauma may develop prior to adolescence. Inasmuch as ample clinical evidence concerning the incidence of descent at adolescence is lacking in true cryptorchidism, final evaluation of the expectant treatment is not permitted (14).

ENDOCRINE THERAPY

In this type of treatment one considers the employment of three forms of endocrine preparations: *a*) thyroid substance; *b*) gonadotropic preparations; and *c*) androgenic substances. Hamilton (14) believes endocrine preparations may effect descent only in those instances wherein relative hormonal deficiencies exist and in which no anatomical barrier to the progression of the testicle is existent. The use of endocrine therapy of cryptorchidism requires consideration of the following factors: evaluation of the functional status of cryptorchid testes prior to adolescence; appreciation of the pharmacological effects and limitations of diverse endocrine preparations administered for comparatively long periods of time; and the possible effects on scrotal structures which may alter the subsequent surgical status of the cryptorchid patient.

Thyroid substance. Prior to 1930, large doses of thyroid substance were employed enthusiastically for cryptorchidism. Although thyroid substance has been regarded by many conservative investigators as being capable of producing serious damage in adolescent patients, Engelbach (32) observed no deleterious effects from large doses of it in cryptorchidism. Recently, favorable reports on the use of small doses of thyroid substance in cryptorchidism have been submitted by Kreutzmann (33) and Meaker and Vose (34). Weisman (12) has found thyroid substance efficacious as supplemental therapy to gonadotropins in the treatment of cryptorchidism.

Gonadotropins. Since the initial report of Shapiro (35) in 1930 and the confirmation of his findings experimentally in monkeys by Engle (36) in 1932, many studies of the therapy of cryptorchidism with gonadotropins have appeared. The majority of these has been concerned with the therapeutic employment of three gonadotropins, chorionic, pituitary and equine. Critical evluation of endocrine therapy of cryptorchidism by Thompson and Heckel (24) has revealed that one of five cases of retained testes may respond to this form of treatment.

Favorable responses to therapy of cryptorchidism with chorionic gonadotropin have been reported by many investigators (24–31, 37–89). In a comprehensive analysis of all published reports, Thompson and Heckel (24) in 1939 estimated that the rate of successful response was 61 per cent. This figure, however, was considerably higher than that from their own critical investigations. In a series of 28 patients less than 16 years of age, Thompson and Heckel induced descent in 9 of 33 cases of undescended testicles, a rate of 27 per cent. In 60 instances of cryptorchidism of all ages, they reported favorable responses in but 17 per cent, the lowered rate of successful outcome being explained in part by a more careful differentiation between migratory and retained testes.

The dosage of chorionic gonadotropin employed commonly varies from 100 to 500 R.U. injected daily or several times weekly. Bigler, Hardy and Scott (57) believe favorable responses will ensue from treatment with a total of 4000 R.U. of chorionic gonadotropin. Sexton (29, 66), Zelson (28) and Wilson (79) have noted successful descent following dosages of

5000 to 10,000 R.U. of chorionic gonadotropin injected over a period of 10 to 20 weeks. Careful observation to prevent the production of precocious maturity or excessive genital growth (24, 30, 64, 65) should be instituted and therapy discontinued if unfavorable responses are obtained. Although most observers (20, 30, 80–90) believe endocrine therapy of retained testes results in growth of scrotal structures favorable to subsequent surgical intervention, the recent studies of Eisenstaedt, Appel and Fraenkel (90) suggest that operative interference is rendered more difficult by preoperative endocrine therapy owing to the development of adhesions and to degeneration of the retained testes. Further investigation is necessary before conclusions concerning the status of chorionic gonadotropin in the therapy of cryptorchidism can be evaluated.

Pituitary gonadotropin has been employed in the therapy of cryptorchidism (29, 84). It has apparently no particular advantage over the chorionic gonadotropin. Available commercial preparations are lacking in potency comparable to the preparations of the chorionic gonadotropin.

Successful therapy of cryptorchidism with the equine gonadotropin has been reported recently by Kunstadter (92). He believes the optimal dosage ranges from 50 to 100 (Cole-Saunders) R.U. intramuscularly 3 times weekly.

Androgens. Inasmuch as gondaotropic preparations doubtless exert some of their effects in the therapy of cryptorchidism by stimulating testicular secretion with subsequent development of the accessory sex organs, therapy of cryptorchidism with androgenic preparations has been investigated by Bauer and Koch (93), Hamilton and Hubert (94) and Zelson and Steinitz (95). Hamilton (14) concludes that results of androgenic therapy of cryptorchidism are discouraging and that gonadotropic preparations represent the treatment of choice whenever endocrine therapy is considered, a view shared by Talbot and Talbot (96), Thompson (30) and Weisman (12). Adequate data concerning the effects of androgenic substances upon spermatogenesis in the descended testicles are lacking.

In a comprehensive analysis of the present status of endocrine therapy of cryptorchidism, Thompson (30) has concluded that chorionic gonadotropin induces descent of those testes which would descend normally at adolescence, an opinion shared by Drake (97), Browne (98) and Johnson (99). However, Thompson (30) has advocated endocrine therapy of cryptorchidism for three reasons: *a*) Early endocrine therapy of cryptorchidism differentiates those cases due to hormonal deficiency and those due to anatomic barriers, identifying therefore, those patients who will require subsequent surgical intervention. *b*) Endocrine therapy at an early age induces scrotal deposition of ectopic testes in 20 to 25 per cent of all patients, thereby, circumventing possible harmful effects of the prolonged ectopic location on gonadal function. *c*) Preoperative therapy with endocrine preparations facilitates surgical interference by stimulating growth and development of various scrotal structures.

Surgery. If endocrine therapy of cryptorchidism proves ineffective, surgical treatment is recommended by Denning (100), Duncan (101), Courtney and Duncan (102), Schuck (103), Turner (90), MacCollum (104), Wohl (105), Thompson (30), Hamilton (14) and others. The results concerning subsequent testicular growth and spermatogenic function following surgical therapy of ectopic testes are inconclusive (29, 106).

SEMINAL FAILURE DUE TO EXTRA-ENDOCRINE CAUSES

Attention to the diverse underlying extra-endocrine factors is a part of the rational therapy of seminal failure. This may include the correction of foci of infection; therapeusis of acute and chronic debilitating states; correction of anemic levels; therapy of metabolic disorders; correction of vitamin deficiencies; an adequate and well-balanced diet especially rich in lean meats and foods containing the essential amino acids; assurance of adequate physical activity; restriction of or abstinence from alcoholic beverages and tobacco; increased exposure to sunlight (107), avoidance of nervous strains and stresses; prolonged vacations, preferably of the out-door variety; and limitation of sexual activity, when it is relatively excessive.

SEMINAL FAILURE DUE TO THYROID DISEASE

When there are lowered basal metabolic levels, thyroid substance often proves to be effective therapy (33, 34). The explanation for the favorable response of hypothyroid patients to thyroid therapy is obscure. In a study of 53 male sterility patients, Hamblen, Pullen and Cuyler (108) observed that the seminal values, as judged by present diagnostic criteria, of patients with a moderately lowered basal metabolic rate were better than the seminal values of sterility patients in whom the basal metabolic rate was normal. Thyroid therapy may produce several desired effects: *a*) alterations in local tissue metabolism subsequent to improved oxygen metabolism; *b*) discharge of constitutionally improved spermatozoa; *c*) indirect effects on gonadotropic activation mediated via the pituitary gland; and *d*) direct alterations in thyro-gonadal relationships.

Medical and surgical therapy of hyperthyroid states may permit restoration of adequate seminal function.

SEMINAL FAILURE DUE TO ADRENAL DISEASE

Alterations may occur in testicular function secondary to faulty electrolyte, water and glucose metabolism. The efficacy of cortical adrenal extract or desoxycorticosterone acetate in the therapy of this type of seminal failure has not been established. Recent experimental studies (109), however, have demonstrated that cortical adrenal extract may stimulate growth and subsequent spermatogenic activity in the testes of male rats.

Adrenogenitalism, resulting either from tumors or hyperplasia of the adrenal cortex, may impair spermatogenic function by a two-fold mechanism: *a*) indirect alterations of the pituitary-gonadal axis mediated via the pituitary; and *b*) germinal failure induced by the excessive androgenic substances. Surgical therapy of the adrenogenitalism may permit the return of normal spermatogenic activity.

SEMINAL FAILURE DUE TO PITUITARY DEFICIENCY

Although the existence of seminal failure due to inadequate gonadotropic activation from the pituitary has been presumed from both experimental and clinical observations, factual proof that pituitary deficiency may induce seminal failure without concomitant androgenic failure is lacking. Diverse types of gonadotropic therapy have yielded varying results, the majority of which is disappointing.

Chorionic gonadotropin. Although the chorionic gonadotropin is assumed generally to activate chiefly the interstitial cells of the testes, favorable reports concerning its therapeutic employment in diverse grades of seminal failure have been submitted by Brosius and Schaffer (110), Charny (111), Heckel (112, 113) and Lloyd (114). In a group of 20 patients manifesting azoöspermia, oligospermia and necrospermia treated with chorionic gonadotropin, Heckel (113) reported that pregnancies resulted in the wives of 4 patients. He concluded that therapy of seminal failure with the chorionic gonadotropin may influence favorably the number and viability of the spermatozoa. Valerio (115) observed striking improvement in a group of 25 men manifesting azoöspermia following combined therapy with 5 cc. of whole pregnancy urine and 2 cc. of adrenal cortical extract thrice weekly for 2 months, although he did not state the incidence of resulting pregnancies. In a study of 6 normal men subjected to therapy with chorionic gonadotropin, Rubinstein (116) noted a pronounced increase in the spermatozoal count, although no alterations in the morphology, motility or viability of the spermatozoa were observed. On the other hand, McCahey (117), Kreutzmann (33), Weisman (12) and others have found the therapy of seminal failure with chorionic gonadotropin disappointing.

Experimental studies reveal equally conflicting conclusions concerning the activation of germinal epithelium with chorionic gonadotropin. Favorable responses with chorionic gonadotropin manifested by the proliferation of the germinal epithelium have been noted in the immature normal rat (118–124), but spermatogenic activity has neither been produced (120, 122, 125) nor augmented (118, 123, 124). On the other hand, spermatogenesis has been initiated by chorionic gonadotropin in the adult lizard (128) and the normal adult ground squirrel (129) during the non-breeding season and in the immature lizard (128) and immature ground squirrel (129). Later studies (130) disclosed that spermatogenesis could be initiated and maintained by chorionic gonadotropin in both immature and adult hypophysectomized ground squirrels. The alterations in testicular structure which have been observed in both normal mature rats (124) and normal immature rats (125) following therapy with chorionic gonadotropin, are an increase in the weight of the testes, an enlargement and widening of the tubules and proliferation of the germinal epithelium without influencing spermatogenic activity.

Pituitary gonadotropin. The available commercial preparations of pituitary gonadotropin are lacking generally in potency comparable to the chorionic gonadotropin. Therapy with the pituitary gonadotropin yields results similar to those obtained by chorionic gonadotropin (113). Moench (131) reported varying degrees of improvement in spermatogenic activity in his group of patients treated with pituitary gonadotropin, a few of whom successfully impregnated their wives following therapy. Hotchkiss (132) observed considerable improvement in the seminal values of 3 patients treated with pituitary extracts and chorionic gonadotropin, 2 of whom subsequently were proven fertile.

Follicle-stimulating gonadotropin from menopausal or castrate urine. Improvement of spermatozoa morphology, count and motility in 9 of 10 men treated with follicle-stimulating gonadotropin from menopausal or castrate urine was reported by Huberman, Israeloff and Hymowitz (140). However, no pregnancies resulted.

Equine gonadotropin. Clinical reports concerning the efficacy of equine gonadotropin in the therapy of seminal failure permit no definite conclusions. Rea (20) and Charny (141) have shown that equine gonadotropic therapy induces a normal histologic appearance of the testicle; in 3 of 5 patients treated, Charny (141) observed moderate improvement in the spermatozoal count. Employing equine gonadotropin, Looney (142) reported gradual restoration of seminal values in one patient manifesting oligospermia. Disappointing responses to therapy of seminal failure

with equine gonadotropin were observed by McCullagh and McGurl (143) and Kreutzmann (33).

Pituitary 'synergist' and chorionic gonadotropin. No detailed studies of the use of this combination therapy have been reported. A few patients, in our clinic, who had failed to respond to other gonadotropins have shown some improvement from the use of this type of therapy.

It is apparent, therefore, that gonadotropic therapy of seminal failure is at present disappointing. This may be due to *a*), the ineffectiveness of available commercial gonadotropic preparations; *b*), the infrequence of pituitary deficiency as a cause of impaired seminal function; and *c*), intrinsic testicular non-responsiveness, which cannot be evaluated by present diagnostic methods. If, in light of the above experiences, a trial of gonadotropic preparations for therapy of seminal inadequacy be considered, a suggested schedule has been outlined in the preceding paper (1).

SEMINAL FAILURE DUE TO INTRINSIC TESTICULAR INADEQUACY

Intrinsic testicular non-responsiveness may be due to diverse factors such as *a*) developmental inadequacy; *b*) local urologic disease; *c*) physiologic immaturity or senility; *d*) damage from roentgen-rays or radium; and *e*) alterations produced by surgery. Rational therapy for these states includes expectant treatment and institution of indicated urologic measures. Should these prove ineffective, the existence of a germinal failure must be accepted. The endocrine failure may be handled adequately by substitutional therapy.

Equivocal results have been reported concerning the value of androgenic preparations in the therapy of germinal failure of both man and the experimental animal. The *modus operandi* of this therapy is obscure but it may be related to a two-fold mechanism, *a*), the production of qualitative and quantitative alterations in the pituitary-gonadal axis mediated via the pituitary; and *b*), the occurrence of local alterations in testicular growth and development which may permit more adequate responsiveness to intrinsic gonadotropic activation.

The use of androgenic substances in experimental animals has produced confusing data, the majority of which cannot be correlated with human investigation. At an early stage in the study of the pharmacology of androgens, it was observed that administration of an extract of bull testes produced injury to the testicular tubules of immature rats (148, 149). Similar effects also have been noted from the administration of androsterone (150, 151), testosterone (152, 153) and testosterone propionate (152–156). These effects may be related either to depression of the gonadotropic fraction of the anterior pituitary by the androgenic preparations (157) or to gonadal atrophy developing as a consequence of non-specific damage (158). Recent studies (159) in rats and mice indicate that small doses of testosterone propionate cause decreases in testicular weight while large doses have no such effect.

On the other hand, small doses of testosterone propionate administered to immature rats for a short period of time (5 micrograms daily for 10 days) are reported to have produced no testicular damage (160) but possible increases in weight (160, 161, 162), the explanation for the weight gain being related possibly to vascular congestion or to fluid increase concomitant with stimulation of the germinal epithelium (160).

Spermatogenesis has been initiated by androgens in the ground squirrel (129) and in the immature rat (163, 164). In instances in which spermatogenesis in immature rats had been inhibited by small doses of testosterone propionate, normal spermatogenic activity was resumed within 7 to 10 months following cessation of therapy (156) demonstrating that there was no permanent injury. It has been shown that administration of androgenic substances will maintain spermatogenesis in the hypophysectomized rat (11, 127–166), mouse (168) and rabbit (169) and that it will not accomplish this in the hypophysectomized guinea pig (170) and monkey (171). When injections of androgenic substances were delayed for 21 days postoperatively, failure to reinitiate spermatogenesis in the hypophysectomized rat (163) and mouse (168) was observed.

The production of oligospermia in a patient 67 years of age treated with daily subcutaneous injections of 10 to 25 mg. of testosterone propionate was observed by Heckel (172). Upon cessation of therapy, restoration of the spermatozoal count ensued, but it was depressed again upon resumption of therapy. Similar observations in 3 patients were reported by McCullagh and McGurl (173), the production of azoöspermia being noted in one patient. Although their follow-up studies (143) revealed no evidence of permanent damage to spermatogenesis, they advised caution in the therapy of seminal failure with androgenic preparations, noting that dosages of 25 mg. thrice weekly of testosterone propionate effected pronounced depression of the spermatozoal count. Decrease in the spermatozoal count ascribable to therapy with larger dosages of testosterone propionate has been observed likewise by Hamilton and Wolfe (174), Kenyon (185), Rubinstein and Kurland (160) and Heckel (176). Heckel and Steinmetz (177) observed no alterations in the volume of the seminal fluid in their group of patients treated with testosterone propionate. On the other hand, Rubinstein and Kurland (160) observed definite increase in the spermatozoal count of 5 normal men treated with 5 mg.

of testosterone propionate thrice weekly. They reported likewise that one patient with lowered spermatozoal motility improved sufficiently from therapy with 5 mg. of testosterone propionate thrice weekly to impregnate his wife several months later. Administering 5 mg. doses of testosterone propionate Kreutzmann (32) observed no alterations in the percentage of abnormal forms in 3 patients with an increased number of abnormal spermatozoa.

SUMMARY

1. Seminal failure without androgenic deficiency exists commonly in many patients. It is unlikely that hypogonadotropic function of the pituitary exists in these patients for, if that were true, evidences of androgenic deficiency would accompany the seminal inadequacy.

2. The causes of germinal failure of the testes have been presented together with methods of differentiation and therapy of the etiologic factors.

3. Therapy of cryptorchidism is indicated for the circumvention of existing or anticipated sterility and subsequent androgenic deficiency.

4. The most beneficial therapeutic schedules for seminal inadequacy are hygienic measures, sexual rest and thyroid substance in appropriate cases.

5. Therapy of seminal inadequacy without androgenic deficiency with present available gonadotropins is uniformly disappointing.

6. No conclusions can be drawn from present data concerning the efficacy of androgenic substances in treatment of seminal failure.

7. Recovery of function in cases of germinal failure secondary to intrinsic testicular non-responsiveness in the majority of instances, cannot be achieved and sterility must, therefore, be accepted.

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Endocrine Aspects of Mongolism

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WHEN, IN 1886, Pierre Marie discovered the relationship between acromegaly and a 'dysfunction' of the pituitary gland, he freed acromegaly from the concept prevalent in his day that the ancestors of the present generation were all giants, and that acromegaly represented an atavism—a retrogression to the giantism of early mankind. When Langdon Down (1), in 1866, published his classic paper on 'Ethnic Classification of Idiots' describing mongolism for the first time, he was influenced by that same dogma; and he was much concerned with the 'philosophical interest' attached to his observation because he felt that mongolism is 'an example of retrogression which furnishes some argument in favor of the unity of the human species.' While acromegaly has long been removed from the field of speculative mythology, mongolism still remains in that field, and relatively few sound attempts have been made to elucidate its fundamental nature. This is the more regrettable since the medical and economic importance of mongolism exceeds by far that of acromegaly. Whereas this latter disorder is rather rare, Bleyer has calculated the number of mongoloids in the United States to be at least twenty-eight thousand. One or two of each thousand newborn infants is a mongoloid.

Mongolism is characterized by a number of outstanding physical stigmata and invariably by a rather high degree of mental deficiency. So striking are these characteristics that anyone who is even slightly familiar with the disorder can select the mongoloid child out of hundreds of other mentally deficient children merely by casual inspection. It is not so much the famous epicanthal fold which characterizes the mongoloid child as it is his peculiar build: his head, his neck, his short extremities, and his heavy, long trunk. The general configuration suggests at sight the operation of abnormal endocrine factors in the genesis of the condition but some writers doubt the fundamental significance of the endocrine stigmata. They believe the cardinal feature to be the mental deficiency and such endocrine aberrations as exist to be secondary results of defects of the central nervous system.

This argument, however, is by no means compelling, since other types of idiocy and imbecility are not usually marked by evidences of hormonal defects. In a comparative postmortem study of 100 mentally deficient children, I found evidence that even in cases of severe malformations and gross defects of the brain, the function of the endocrine glands is surprisingly independent of anatomic lesions in the brain. The only exception is focal pathology of the surroundings of the third ventricle and the hypothalamus which causes a well-defined endocrine disorder.

Mongolism is due to a prenatal developmental disorder which, unlike that of classic cretinism, is plainly evident at birth. Because of this fact, the study of the condition involves two different problems which are often confused in the literature. The antenatal developmental deficiency cannot depend on any endocrine organ or organ system of the embryo, because some of the malformations which are sometimes found to be associated with mongolism (septum defects of the heart, syndactyly, abnormalities of the hand lines, developmental deficiencies of the central nervous system) indicate pathological factors at work as early as in the second and third month of fetal life, at which period the endocrine system of the embryo has not yet developed. Thus the mongoloid deficiency is due either to a general germinal inferiority or to noxious agents within the maternal organism. That the latter possibility demands serious consideration is shown by the recent work of Benda, Dayton and Prouty (2), who have brought forth evidence that mongolism is correlated with an abnormal response to impregnation, the mother being at the threshold of hormonal sterility.

We may now examine, the second problem, the postnatal development of the mongoloid. Do the anomalies that are present at birth explain the abnormal course of development thereafter? The advocates of germinal inferiority say that the mongoloid is a different being, a unique 'species' due to an unknown whim of nature, a 'mutation' of the human

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race. They assume that the child develops in a different way because of its different constitution, and no pathology of any special organ or organ system need be looked for.

It is a striking and seemingly paradoxical fact that the postnatal evolution of the disorder does follow patterns that are closely paralleled in certain endocrinopathies—a fact that I have determined from a study of 38 cases at post-mortem and 250 living subjects. Obviously, the presence of a pathologic etiological factor acting in the postnatal period is suggested. Why has this peculiar pathology not been hitherto recognized?

If mongolism were an ordinarily progressive disease, the child would invariably die in the terminal period of it, and the investigator would be in a position to establish its main pathology with the same degree of accuracy as in the case of any other chronic disease. But the mongoloid baby is born as a mongoloid, and if it does not die shortly after birth, it usually continues to live for 10 to 20 years and then dies of some intercurrent disease, usually tuberculosis. Since an extreme degree of endocrine imbalance, as is seen for instance in Simmonds' cachexia, is not compatible with life, it follows that the mongoloid child must have established a fair amount of endocrine and metabolic equilibrium. Some sort of secondary compensation for the primary deficiency must have been achieved. Hence we could hardly expect to find definitive evidence of the initial essential pathology in a mongoloid patient who dies 10 or 20 years after birth. On the other hand, in mongoloid babies who die a few days or a few months after birth, the unobscured pathologic processes which are related to the fundamental deficiency of mongolism, might be detected. Moreover, those children who are not able to live may reveal more marked degrees of the same deficiency that is present in all of them.

What is mongolism at birth and what is its later evolution? Although experienced obstetricians and pediatricians are able to make the diagnosis at birth, one might emphasize that only the very experienced are able to do so, and probably not more than 50 per cent of mongoloid babies are actually recognized so early. If one analyzes the characteristics of the mongoloid baby, one finds that the most outstanding feature is a retardation of the development of the skull, the sutures of which are more or less gaping, while the skull is shorter and the circumference is smaller than normal but still within the limits of normal variation. The forehead is high and round—not absolutely, but in relation to the underdevelopment of the nasion and the maxilla. The body does not appear peculiar in any way except for the hands, which are sometimes more wrinkled, and the feet, which show a gaping between the first and second toes. There is some flabbiness of the joints from the very beginning. It seems to me that at birth, the most outstanding feature is the skeletal developmental deficiency which I have called, in contrast to acromegaly, 'congenital acromicry.' Indeed, all those parts which we see hypertrophied in acromegaly are underdeveloped in mongolism and remain so in later life. The epicanthal fold is due to the shortness of the nasal bridge; the eyes slant upwards externally. I feel sure that the explanation of this slanting is a failure of the zygomatic processes to grow at the normal rate, with the result that the orbits remain egg-shaped. The so-called 'mongoloid look' has nothing to do with racial characteristics and is due to anomalies of the skull development.

At birth, and shortly after, the mongoloid child appears very quiet, and mothers state that their mongoloid children are the best babies of all because they sleep so much and are never 'fussy.' Psychological tests show that the mental deficiency, as far as it is possible to test it, is not so marked in the very beginning.

The fact which has escaped the attention of previous investigators is the developmental failure of the mongoloid baby *directly after birth.* During the first 6 months, the baby shows an almost complete arrest of growth. He loses weight and remains at the same weight for several months. At the end of the first half-year, and frequently at the end of the full year, he weighs 12 to 15 pounds only. The skull which should enlarge rapidly, does not grow, and the whole development is stationary. If one compares a mongoloid baby of 9 months or one year with a normal child, one is likely to estimate the age of the former at 2 or 3 months. The main feature is, therefore, not so much a striking 'mongoloid' appearance as a complete developmental arrest after birth. One might summarize and say that the mongoloid baby is not able to adjust itself to the conditions of extra uterine existence. Some agents which go into action in a normal child after birth, and which foster its rapid development seem to be lacking in the mongoloid.

From a nutritional point of view, the majority of mongoloid babies are malnourished, which is quite in contrast to the quick and steady gaining after the first year. The mongoloid features become very marked by the end of the first year because of the striking contrast between the mongoloid and the normal child. The latter has completed a number of developmental changes of its skull and body, while the acromicry of the mongoloid becomes even more striking every month. If the mongoloid child does not die in the first year and does not contract a chronic or intercurrent disease, he develops better in the following years, gaining in weight, even becoming over-

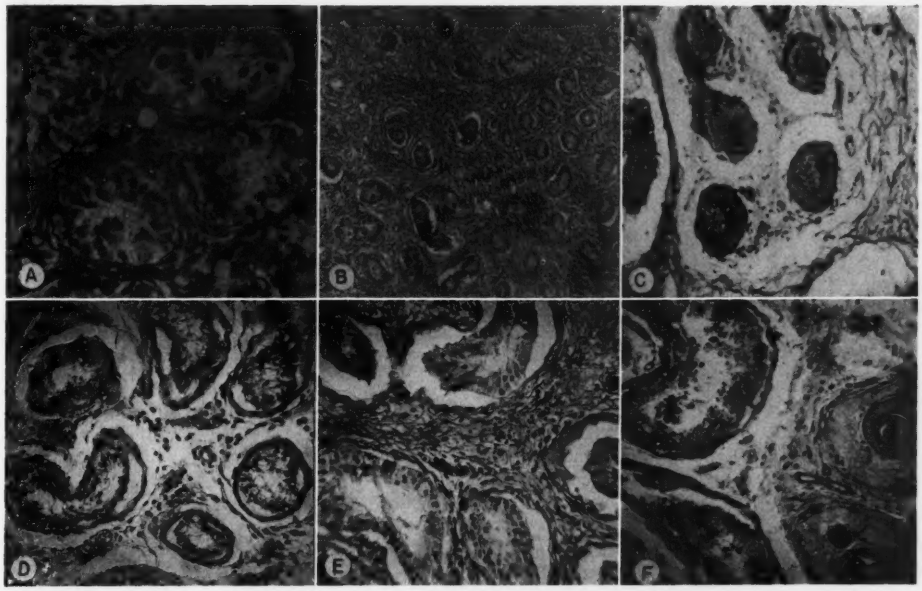

Fig. 1. MALE GONADS IN MONGOLISM. *A.* TESTICLE of 5-month-old mongoloid baby. The seminiferous tubules are close together. They are filled with a syncytium of Sertoli cells which represent the majority of all cells present. Note that in each tubule, there are 1 to 3 larger cells, spermatogenic cells. This picture is essentially normal for that age. *B.* TESTICLE of 23-month-old mongoloid baby. Note the striking increase in coarse interstitial connective tissue separating the tubules from each other. Some tubules appear encroached upon and degenerated. Several tubules still contain 'germinal epithelium' embedded in the Sertoli syncytium. *C.* TESTICLE of 16-year-old mongoloid boy. The tubules contain only degenerated Sertoli cells which fill the entire lumen. No spermatogenic cells present. Note the increase in interstitial fibrous tissue, which is loose and edematous. No interstitial cells present.

D. TESTICLE of 20-year-old mongoloid adult. Note the thickening of the basement membrane. Tubules filled with Sertoli cells. No spermatogenic cells. *E.* TESTICLE of another 20-year-old mongoloid adult. Note the coarse fibrous tissue separating the tubules. No interstitial cells. The tubules have a lumen. There are Sertoli cells and some primary spermatocytes but no mature sperm cells. *F.* TESTICLE of 31-year-old mongoloid dwarf (4 ft., 8 in.). Note thickening of basement membrane and increase in loose edematous connective tissue. Tubules contain Sertoli cells and primary spermatocytes but no maturing spermia. Note large amyloid bodies in degenerated tubules at right.

weight. The rate of growth is almost equal to the normal growth rate, but since the mongoloid has lost about a whole year at the start, he never is able to catch up with normal children. A correlation chart made for mongoloid children who came to post-mortem examination showed that those of an age group between 9 and 14 years show retardation in growth of 2 to 5 years. The mongoloid adults beyond puberty showed a maximal physical development of 12-year-old children, with the exception of 3 who were 'borderline' cases.

The mongoloid boy at puberty develops pubic hairs which are long and silky and of the female type of distribution. Not one of 7 mongoloid males above the age of 15 which we have studied showed a normal escutcheon. The penis is usually long and thin and monkey-like. The testicles are frequently undescended or extremely small. Sometimes they may appear normal, but microscopic examination reveals evidence that they are chiefly composed of fat and fibrous tissue and the glandular parenchyma is sparse. In only one case in our autopsied series was spermatogenesis found, and this was a case in which there was some doubt of the diagnosis.

As stated before, the trunk is heavy and long and the extremities short with the fingers broad and clumsy in the majority of cases. In some cases, however, the fingers remain short and small like those of small children. The neck is usually heavy, which is due to the flattening of the occiput and to an underdevelopment of the vertebrae. The vertebra column is frequently rather straight.

The mongoloid girls show an even more marked retardation in physical development, and most of them show arrest at a level of 9 to 10-year-old children. Approaching puberty, they develop large breasts but with flat nipples and complete absence of the areola and Montgomery glands (3). The pubic hairs are scarce and axillary hairs are usually absent. The labia majora are large and rounding, while the labia minora are underdeveloped, or almost absent The clitoris is frequently protruding and hyper-

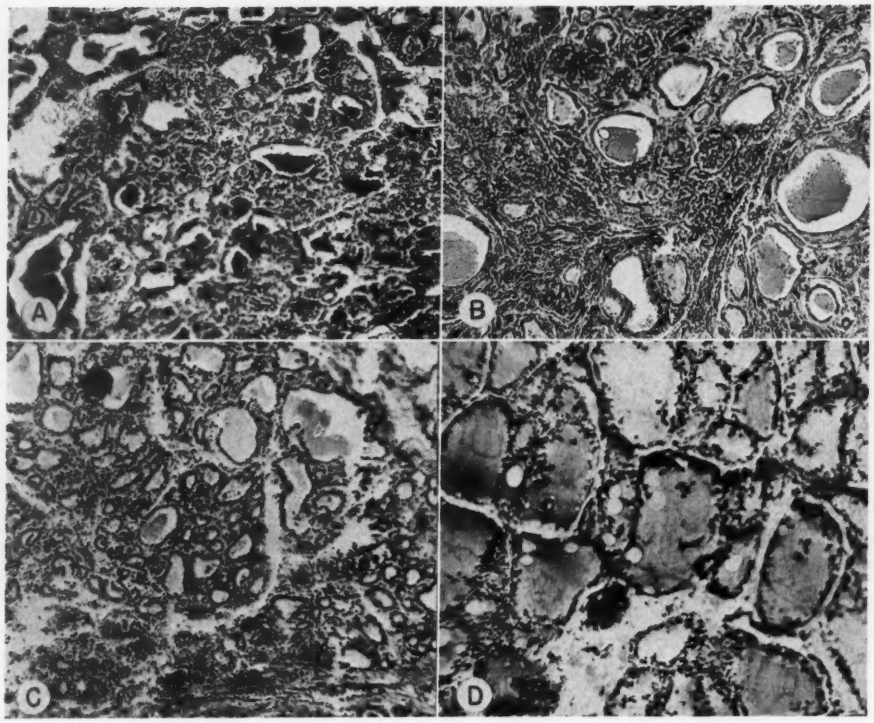

Fig. 2. THYROID IN MONGOLOID BABIES. *A.* THYROID of 2-month-old mongoloid male baby. Note irregular unfolding of follicles. Large areas are filled with microfollicular parenchyma without colloid, irregular cell growth and cell degeneration. Several follicles are enlarged, crowded and irregular in shape. They are filled with dark-staining, brittle colloid. Epithelium flat. *B.* THYROID of 9-month-old mongoloid baby. Marked fibrosis and degeneration of microfollicular parenchyma. Irregular unfolding of some follicles with colloid. Completely flattened epithelium.

C. THYROID of 9-day-old mongoloid baby. The microfollicular parenchyma is irregular and without colloid. Increased fibrosis. Some follicles distended with irregular shape and flattened epithelium. *D.* THYROID of 7-month-old mongoloid female baby, the youngest patient with a hypoplastic diffuse colloid goiter. All follicles distended to an average size of 250–350 microns. (Some had follicles of a size up to 500 microns.) All epithelial walls flattened. Follicles filled with brittle colloid. Interstitial tissue degenerated by compression. Colloid diffusion into spaces.

trophic. Menstruation is established in more than 50 per cent of the mongoloid girls, but the menarche is frequently delayed. Menstruation may cease entirely after several years.

Mongolism differs from cretinism with regard to the skin, subcutaneous tissue and the development of the skull and bones. The mongoloid skin is elastic and smooth, and the circulation is visible through the cutis. In some cases, myxedema develops secondarily. Many mongoloids show marmorated skin. The subcutaneous fat tissue is overdeveloped, but, at the same time, the musculature of the mongoloid is well developed and strong. The skull of the cretin is relatively large and the ossification is delayed. In mongolism, the appearance of ossification centers is not delayed, but they increase very slowly in size.

From a clinical point of view, we see in mongolism an immaturity of the development of the sex organs with absence of the secondary sex characteristics. There is a tendency to obesity. There is general immaturity and retardation in growth with its early final cessation. The cartilage of the distal epiphyses degenerates, but there is definitely no premature ossification. Histologic studies show the presence of cartilage remnants after growth has ceased (4). The mongoloid patient, in short, shows numerous characteristics which parallel those of gonadal underdevelopment, adrenal cortical dysfunction, thyroid dysfunction and pituitary dysfunction; but the mongoloid deficiency does not fit precisely into any of the classical categories. It has been the purpose of a careful pathologic examination to throw some light on this complicated condition and to explain the peculiarities which distinguish this condition from those diseases which are better known.

Our pathological observations are based on a series

of 38 cases. Details of the pathology will be given in another publication, but the main observations may be summarized here.

Our thymus material is not sufficient to permit definite conclusions. This gland was hypoplastic in most of the cases with one exception—that of a 12-year-old girl in whom it weighed 15.7 gm. The histologic examination did not reveal conspicuous anomalies in any case. We may, therefore, conclude that the thymus in mongolism is hypoplastic but that no consistent pathology is evident.

The adrenal in mongolism appears normal (5) in the first year of life, but after the lapse of that time, it shows a marked retardation of development of the outer cortical layers. These remain small, and the zona fasciculata especially is very narrow. In many cases, the reticularis covers a space larger than the two outer layers together. Conspicuous is the lack of lipoid material in the zona fasciculata. The medulla appears to be well developed.

The gonads appear normal in young mongoloids. They show the same arrangement of Sertoli cells in the testicles as is seen in normal infants, with one or two germinal mother cells—so-called 'male eggs' in each tubule. With the approach of puberty, immaturity of the testicles becomes conspicuous. In 7 cases of mongoloid males above the age of 15 years, the majority showed immature tubules tightly filled with Sertoli cells without spermatogenesis. In a few cases, primary spermatocytes were observed, but more progressive stages could not be found. There was one case only in which complete spermatogenesis was present. At the time of death, the boy appeared only slightly 'mongoloid' and there was considerable doubt as to the diagnosis. In his earlier years, however, the boy had shown several typical features of mongolism such as short, wrinkled hands, the prominent, flabby and underdeveloped ears, a puggy nose and flat face. This case is of importance when the question arises as to whether or not a mongoloid boy should be sterilized. Our autopsy material shows that the faculty of mongoloids to produce children is almost *nil*, but this one instance suggests that in so-called borderline cases, maturation of the testicles may occur, and these cases need special consideration.

The ovaries of the mongoloid females appear normal in babies and young infants, but at the age of 8 to 10 years, they show a strong tendency to cystic degeneration, with destruction of the primary Graafian follicles. It is worth while to mention that the ovaries of some of the girls of 8 to 12 years showed an unusual number of atretic follicles and scars. The anatomic picture suggested almost a short phase of ovarian hyperactivity with subsequent exhaustion, and not a state of mere 'hypofunction.'

TABLE 1. CONTRAST OF CHARACTERISTICS OF ACROMEGALY AND MONGOLISM

Acromegaly	Acromicria Congenita (Mongolism)
Increased growth of prominent parts (acromegaly)	Hypoplasia of prominent parts (acromicry)
Increased pneumatization of skull	Absence or underdevelopment of sinus system
Increase in diplöe of flat bones	Underdevelopment of diplöe
Increased cartilage activity	Decreased cartilage activity
Splanchnomegaly	Splanchnomicry
Genitomegaly	Genitomicry
Thyroid hypertrophy	Thyroid hypoplaisa
Hypertrophy of adrenal cortex	Hypoplasia of outer cortical layers
Hair abundant and thick	Hair scant and thin
Increased pigmentation	Lack of pigmentation

The pathology of the thyroid is summarized in tables 2 and 3. In table 2, the weight of the thyroid is given in order to demonstrate the marked hypoplasia of this gland in mongolism. The hypoplasia is very impressive at autopsy. As a matter of fact, it is frequently difficult to find the thyroid in mongoloid children, and the recorded weight includes that of the capsule and connective tissue which could not be separated without microscopic dissection. The weights are, therefore, too high, but even so they indicate underdevelopment of the gland. There are very few careful observations on the weight of the thyroid of normal persons. For the adult thyroid, a weight of 20 to 30 gm. is considered normal, and for the newborn, a weight between 2 and 3 gm. is normal. I am not aware, however, of any data on the normal thyroid weight during infancy and childhood. Although it is stated that in feeble minded adults or

TABLE 2. WEIGHT OF THYROID IN MONGOLISM[1]

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Age	Months							Years																
	1.5	2	5	6	7	7	19	4.5	8.7	8.8	9.8	10	12	14.5	15	16	16	17	17	18	20	20	28	31
Sex	F	M	M	F	M	F	M	F	F	M	F	F	F	M	M	M	M	M	M	M	M	M	F	M
Weight, gm.	1.0	2.3	1.1	0.5	2.5	2.0	2.0	1.0	5.0	2.5	4.5	9.8	9.0	7.0	6.0	7.7	11.0	5.0	11.0	3.5	23.0	19.0	5.5	3.5

[1] Including capsule and connective tissue.

TABLE 3. MICROSCOPIC STRUCTURE OF THIRTY-FIVE MONGOLOID THYROIDS

Case No.	Sex	Age	Normal Epithelium, Normal Colloid Content	Struma Diffusa, Parenchymatosa	Struma Diffusa, Partly Microfollicular, Partly Macrofollicular	Struma Colloides, Macrofollicular	Struma Lymphomatosa
1	F	2 days	+				
2	F	9 days			+		
3	F	6 wk.			+		
4	M	2½ mo.		+			
5	M	3 mo.			+		
6	M	5 mo.			+		
7	F	6 mo.			+		
8	F	6 mo.			+		
9	F	6 mo.			+		
10	M	7 mo.				+	
11	F	7 mo.				+	
12	M	8 mo.			+		
13	M	9 mo.		+			
14	F	10 mo.					
15	F	16 mo.				+	
16	F	18 mo.			+		
17	F	4½ yr.			+		
18	M	9 yr.				+	
19	F	9				+	
20	F	10				+	
21	F	10				+	
22	F	12				+	
23	M	14			+		
24	F	14			+		
25	F	14				+	
26	M	15				+	
27	M	16			+		
28	M	16	+				
29	M	17			+		
30	M	17				+	
31	M	18				+	
32	M	20					+
33	M	20			+		
34	F	28			+		
35	M	31				+	

children, the thyroid is frequently underdeveloped, I found it useful to check this statement and to compare the mongoloid thyroid with that of undifferentiated idiots and imbeciles of various sorts. Forty cases were available in which the thyroid was removed and the weight determined under exactly the same circumstances as in the mongoloid autopsies. The results are given in the table 4. Although the values given may be too low for normal children, they prove beyond doubt two facts, *a*) that the thyroid is usually not extremely hypoplastic in uncomplicated idiocy and imbecility, but that it corresponds to a low normal; and *b*), the thyroid of monogoloids is extremely hypoplastic when compared with that of other mentally deficient children. Measurements demonstrate that the hypoplasia varies in its extent, but that it was found in all cases with the exception of two, which will be discussed later. The most extreme degrees of hypoplasia were seen in 4 patients. One mongoloid girl of 4.5 years of age had only 2 small nodules of thyroid tissue with a total weight of 1 gm. on each side of the trachea without an isthmus. In one mongoloid baby the thyroid was absent but some thyroid tissue was found within the thymus. One 9-year-old boy had a thyroid weighing 2.5 gm. and in one 18-year-old boy the gland weighed 3.5 gm. I might mention that in several cases, the thymus and the thyroid were connected with each other, and it was impossible to separate the two without the use of the microscope.

A real understanding of the thyroid pathology is to be gained only through microscopic study. The observations are tabulated in table 3. The terminology used is the same as that used by De Quervain and collaborators (6) and especially Wydler (7). These outstanding Swiss scholars have studied cretinism on the basis of the large material from the canton of Berne. The paper represents the rather authoritative opinion of a large group of Swiss scholars in regard to cretinism. Table 3 shows that the most frequent finding in the thyroid of mongoloid children and adults is a diffuse hypoplastic colloid struma. The histology is given in illustrations (fig. 3, A, B, C). These glands show a uniform picture of enlarged follicles measuring 250 to 500 microns, filled with a colloid which stains dark red or blue; the epithelial walls are flattened; the interstitial tissue has disappeared, and the follicles touch each other. This simple picture of a hypoplastic colloid thyroid was present in all mongoloid girls and in 6 boys. The youngest patients with this type of colloid struma were 2 babies of 7 months. During the first year of life the most frequent picture, however, is a small hypoplastic gland, the periphery of which shows follicles distended with heavy staining colloid and having flattened epithelial walls. The central portion of these thyroid glands shows an increase in connective tissue and an accumulation of small distorted follicles of various size without colloid. The atelectasis of the central nodules is different from the normal infantile thyroid in that the stroma

TABLE 4. AVERAGE WEIGHT OF THYROID OF 40 CONTROL INDIVIDUALS[1]

Age in Years	Thyroid Weight gm.
2–5	2–4.5
8	6
12	8–14
14	12–14
15	12–20
19	17–24
20 and above	12–27.5

[1] Cases of mental deficiency chiefly idiots and imbeciles.

is greatly increased, and the epithelium (parenchyma) shows an irregular proliferation of cells with pycnosis and absence of normal follicle formation. It seems, however, that as time goes on, the atelectatic nodules disappear and are replaced by simple colloid accumulations. In 3 babies, the thyroid was degenerated and did not show colloid formation. In the youngest and smallest baby, that of two days, the thyroid showed unusually high epithelial walls and a periphery with distended follicles containing rather dark colloid. This thyroid was somewhat advanced in its development rather than retarded.

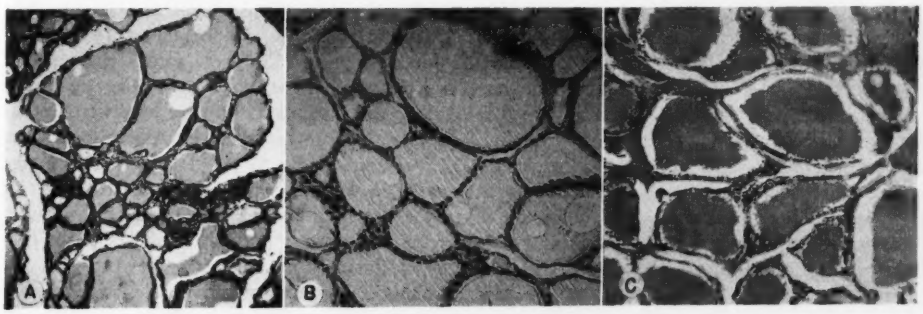

Fig. 3. THYROID IN MONGOLOID CHILDREN AND ADULTS. A. HYPOPLASTIC MACROFOLLICULAR COLLOID GOITER in 28-year-old female. Flattened epithelium. Large follicles with thickened colloid. Little vacuolization. 'Resting' thyroid.
B. THYROID, 10-year-old mongoloid girl. Hypoplastic macrofollicular colloid goiter, "resting."
C. HYPOPLASTIC MACROFOLLICULAR COLLOID GOITER of 12-year-old mongoloid girl. Note extreme flattening of epithelium and colloid diffusion into spaces.

DISCUSSION

The material presented herein proves beyond doubt that mongolism is associated with thyroid pathology. This fact has been suspected for more than 40 years, and yet, no progress has been made in understanding the mongoloid pathology because a discussion of thyroid pathology in mongolism was blocked through the observation that mongolism has nothing in common with cretinism. When the pathology of the mongoloid thyroid was emphasized, the exponents were silenced on the basis that the differences between cretinism and mongolism are obvious, and that biochemical and metabolic studies on mongoloids have so far failed to demonstrate the thyroid pathology. It is, therefore, necessary to discuss the differences between cretinism and mongolism to some extent. As a matter of fact, it is this difference between the two conditions which will greatly enlarge our general understanding of the various types of thyroid pathology. The histology of the thyroid in cretinism is characterized by degeneration of the parenchyma, proliferation of the connective tissue stroma, degeneration and insufficiency of the blood supply, and a deficiency or complete lack, of colloid. It should be emphasized that the cretin struma is free of colloid and that only in a small percentage of cases is colloid to be found at all; if present, it is rather brittle. As Wydler (7) emphasizes, if colloid is present, it is sparse and indicates a previous state of functional activity. These observations refer to the thyroid struma of endemic cretinism. In myxedema and sporadic athyroidism, the thyroid is atrophic or missing, and is not functioning at all. The changes are described by Marine and Lenhard (9) as follows: 'The colloid is practically absent. The epithelial cells have lost their regular and columnar type and are irregular in size and shape. The nuclei are in general large, often hyperchromatic, and irregular in size and outline. Nuclear figures are still observed but the new formation of cells is not sufficient to offset the cell death and the follicles become smaller. The surrounding fibrous stroma is relatively—perhaps absolutely—increased as the follicles become smaller from the death of their secreting cells.' Although the amount of cell death, degeneration, and fibrosis may vary from case to case, the common denominator of all functional inadequacies is the loss of the ability of the follicles to form and store colloid.

In contrast to the thyroid pathology of cretinism and myxedema, the thyroid of the mongoloid is essentially a colloid struma. The thyroid of the mongoloid has the ability to secrete and store colloid, and it is because of this faculty that all biochemical and metabolic studies in mongolism have failed to demonstrate a marked thyroid deficiency. The colloid thyroid (goiter) is anatomically abnormal (9), but conclusions with respect to the function of such thyroids are not justified. They may be 'hyperrhoic,' 'eurhoic,' or 'hyporhoic.' The functional ability of a thyroid can be determined only by biochemical and metabolic studies on the patient. Such studies have been reported by Benda and Bixby (10 in 1939). In

this paper, Bixby reported blood cholesterol values in 50 persons with mongolism, who ranged in age from 2 to 29 years. The values ranged from 135 to 234 mg. per 100 cc., values now accepted as normal. Five of the values (which were those of females) were close to 250 mg., which is a high normal level. One boy of 10 years had on 3 different occasions, values of 312, 291, and 244 mg., respectively. The basal metabolic rates of persons with mongolism were studied in 25 cases, and it was shown that if the Mayo standards are used, all mongoloids had values between −2 and −24, the majority being between −10 and −20. If the Talbot weight standard is used, the majority still showed values ranging between −1 and −21, with the exception of 4 cases who showed low plus values; with the Talbot height standard, the majority were between 0 and −10. From these biochemical studies, the conclusion may be drawn that the function of the thyroid, as far as basal metabolism and iodine metabolism are concerned, is within normal range in mongolism; but the metabolism is 10 to 20 per cent below the average. The hypoplasia of the thyroid, as well as these metabolic studies, discard the assumption that hyperthyroidism might be considered.

While in cretinism, the thyroid has lost its ability to store and secrete colloid and there is degeneration of its secretory apparatus, the thyroid of mongoloids has a well-preserved functional ability but is a 'resting colloid thyroid (goiter).' Knowledge of the mechanism of colloid goiter has been gained recently through many experimental studies on hypophysectomy. Van Dyke (11) summarizes the morphologic changes in the thyroid after hypophysectomy: 'Undischarged colloid accumulation in vesicles lined by flat, inactive epithelial cells.' Salter (12) describes the functional effect of hypophysectomy as follows: 'The basal metabolism falls to 80 per cent of normal, but the organism stops short of clinical myxedema.' This drop of the metabolic rate 'short of myxedema' is exactly what is present in the majority of mongoloid persons, with the exception of a few who develop a real myxedema which is easily mitigated by thyroid therapy. The accumulation of colloid, with a flattening of the follicle walls, and the general hypoplasia indicate, therefore, the lack of stimulation by the thyrotropic hormone of hypophyseal origin. While cretinism is the result of a primary degeneration of the thyroid, which can not react to thyrotropic hormones even when given in excess, the thyroid of the mongoloid child is primarily a normal thyroid which lacks functional stimulation from the pituitary. The thyroid of the mongoloid is essentially identical with the thyroid of the experimentally hypophysectomized animal.

We are, therefore, able to conclude that the endocrine pathology of mongolism is characterized by *a*), hypoplasia of the thyroid with a resting colloid goiter; *b*), by failure of the gonads to mature; and *c*), by a hypoplasia of the adrenal cortex in which the outer layers fail to develop normally and to store lipoid in the zona fasciculata. In all three organs the glandular pathology arises secondarily, due to the lack of stimulation and not to a primary anomaly or disease.

The endocrine pathology in mongolism indicates a functional pathology of the pituitary gland. The question arises as to how much of this functional disorder is the result of anatomic changes of the anterior lobe of the hypophysis.

The number of the specific physiologic effects of the anterior lobe of the pituitary is remarkable, and Collip (13) cites 16 of these specific actions. The cytologists and pathologists have generally recognized only 3 cell types of the anterior lobe, *i.e.*, the chromophobes, the alpha and the beta cells. Some anatomists have expressed the opinion that the chromophobes are 'reserve' cells which have no secretory action. This would leave the whole secretory activity of producing at least 16 different effects to the two cell types, the alpha and beta cells.

The only known anatomic patterns of pituitary pathology are acromegaly, Simmonds' disease and pituitary basophilism; the first being associated with an eosinophilic (alpha cell) adenoma; the second with destruction of all cell elements and the third with an increased number of basophilic (beta) cells. It has been concluded that the eosinophilic cells produce 'growth hormones.' It is beyond the limit of this paper to discuss the conclusiveness of this claim. There are several facts which are not yet settled, but even if we accept the conclusion, that the eosinophilic elements have some relationship to the clinical phenomenon 'growth,' there is no doubt that the relationship between the anatomy of the gland and its physiologic activity is far more complicated.

Experimental pathology has dwelt to a great extent on the relationship between the pituitary and the gonads. There is much experimental evidence that the pituitary reacts to castration with the formation of vacuolated beta cells known as 'castration' cells. Severinghaus (14) draws the conclusion that the data at hand 'tend further to bring the basophils into direct relation to the gonads.'

The effect of thyroidectomy on the pituitary cells seems to vary with the experimental animal species. In some animals, an increase in the number of basophils has been observed with the development of vacuolation similar in appearance to that following castration. For man, it seems more probable that the alpha cells are increased in hypofunction of the thyroid. Erdheim (15) has reported a marked increase of alpha-cells in congenital thyroid hypoplasia.

At present it is safe to conclude that pathology of pituitary function may manifest itself in some anatomic changes, but it is impossible to draw direct conclusions from the anatomy of the pituitary body as to the physiologic potency of its secretory elements. A deficiency may manifest itself in the absence of some cell elements, but a dysfunction in which there is potency of some factors and inadequacy of others can hardly be expected to manifest itself in such simple patterns as the varying distribution of three main cell types, which are concerned with more than 16 different physiologic actions.

With this in mind, it is not surprising that the antithesis of acromegaly, congenital 'acromicry' is not associated with a decrease or absence of eosinophilic elements in cases of congenital acromicry. Almost the opposite is true. In 1939, (16) I published a first report on the pituitary gland in 16 cases of mongolism, and demonstrated that the majority showed an increase in eosinophilic elements. The present report is based on observations of 32 pituitaries in mongolism. The results are shown in table 5. The data confirm in part the former report of a marked increase in alpha cells in mongolism, and establish the fact that pituitary pathology in mongolism is not a uniform histologic picture which can be considered characteristic of that condition.

Histologically, the pituitary gland in mongolism may be one of two main types. The most common is characterized by an increase in alpha cells which occupy the whole field or fill large areas to the exclusion of the other cell types (15 cases.) In 4 additional cases, a rather similar picture was found, but there were many beta cells also (one-third to two-thirds of all cells); these occurred in groups or islands, and showed distinct vacuolation with halo formation around the nuclei, resembling castration cells. This cell type was found in boys above the age of 9 years. The pituitary from the one female, aged 28, also showed an increase in the number of beta cells. Nineteen of 32 cases of mongolism showed, therefore, a predominance of chromophilic elements with almost no chromophobic cells. The second histologic type of pituitary was characterized by a prevalence of chromophobes with only a few other cell types present; one had alpha cells and 3 beta cells, respectively. In 3 cases, the distribution of the various cell elements appeared not unusual.

These observations seem confusing, but if one bears in mind that these patients suffer from the residuals of an early developmental disorder, it is readily understood that the histology of the pituitary not only reflects the pathology, but reflects the varying adjustment of the pituitary to its endocrine surroundings, at the same time. The pathology is indicated by the shift of the pituitary cell types toward the eosinophils and the lack of other types of cells in these glands. In the other group of cases, the general deficiency of the chromophilic cell types is conspicuous

There are several ways of interpreting these findings. If the assumption is made that the alpha cells are related to the production of the growth factor, and if Erdheim's (15) suggestion that the presence of increased alpha cells in aplasia of the thyroid means a compensatory activity of the pituitary is considered, then, the most reasonable interpretation of our observations would be, that in the majority of cases of mongolism, the pituitary is attempting to compensate for the deficiency of the thyroid and is able to produce a fair amount of growth hormones which keep the children growing for about 10 to 12 years. In some cases, there is even a hyperfunction, in which ensuing acromegalic traces are recognizable. In another group of 10 cases, the secretory ability of the pituitary appeared diminished and a state of general pituitary deficiency was suggested by the anatomic observations.

TABLE 5. PITUITARY IN MONGOLISM

Histology of Anterior Pituitary Lobe	Number of Cases
Chromophobes predominant, only few other cells present	6
Chromophobes predominant, scattered alpha cells present	1
Chromophobes predominant, scattered beta cells	3
Alpha cells predominant, almost no other cells	15
Beta cells predominant or numerous; castration cells; alpha cells present	4
Fair amount of all cell types	3
Total	32

If this interpretation is accepted, it is necessary to assume that the growth stimulating capacity of the pituitary is intact, but that the responsiveness of the thyroid, adrenals, and gonads is at fault. It is, however, probable that the eosinophilic reaction in the majority of the pituitary cells does not indicate that these cells are producing growth-promoting hormones. The fact that an increase of alpha cells has been observed experimentally in hyperthyroidism and hypothyroidism and after castration, seems to indicate that the staining reaction is rather unspecific and manifests only a shift in the endocrine balance.

Whatever the final interpretaion may be, the material presented indicates that the pituitary in mongolism is in a state of dysfunction which is the center of a disorganization of the endocrine environment of the mongoloid person.

CONCLUSIONS

On the basis of previous clinical studies and the autopsy material of the 38 cases presented in this report it seems possible for the first time to offer a definition of mongoloid deficiency. As a result of a pathologic gestation period, which either is lacking in some essential hormonal agents or is pathologic due to noxious metabolic factors, the mongoloid baby is essentially immature at birth ('unfinished child'). As a result of the immaturity, the pituitary and thyroid of the mongoloid baby are not able to function properly and to adjust to the conditions of postnatal life. It seems probable that the noxious metabolism damaged the thyroid and pituitary of the baby; this is indicated by the atelectasis and fibrosis of the thyroid and necrosis of most of the pituitary cells which is seen in mongoloid babies. The failure of proper development during the first year is due to the inability of these key glands to function. The dysfunction of the pituitary results eventually in a hypoplastic colloid goiter of the thyroid and in failure of the adrenal cortex to develop normally. The lack of gonadotropic stimulation results further in degeneration and immaturity of the gonads of both sexes. The fact that the mongoloid baby after the first year of life starts to grow and to develop fairly normally for about 10 years is explained through the activity of the pituitary, which appears to develop a capacity for at least a part of its functions. Not before the approach of puberty, which creates new requirements on the endocrine environment of the mongoloid child, does the inadequacy of the pituitary become conspicuous again. At that time, obesity or cachexia occur, and, as the data indicate, the majority of mongoloid patients die in the second decade of life, if they have survived the first year.

The pathology of mongolism is of great importance because of the question as to whether therapy has a reasonable chance of improving the condition of these unfortunate children. Since mongolism is essentially a prenatal deficiency, the main purpose should be to recognize the condition during prenatal care. The paper of Benda, Dayton, and Prouty (2) seems to provide some material which suggests that this goal is not entirely out of reach. At present the best chance to treat the mongoloid is as shortly after birth as possible. Our studies on the mongoloid brain suggest that edema of nerve cells and metabolic changes of the white matter produce early degeneration of the brain, and these changes are not reversible after the lapse of some months. An early treatment will be successful, however, only in a certain percentage of cases. The prognosis of treatment depends on the degree of retardation at birth and the amount of congenital malformations present. The greater the number of malformations such as syndactyly, septum defects of the heart, congenital cataracts, or signs indicative of developmental disorders of the brain and spinal cord, the less favorable the prognosis. On the other hand, some mongoloid babies show only a few markings of retardation, and in these cases, the prognosis is better. Although there are a few encouraging reports in the literature on thyroid and pituitary therapy in the mongoloid, therapy is still in an experimental state, and our pathologic study indicates the complexity of the situation with which the clinician has to cope.

DeQuervain (6) has pointed out, for cretinism, that if only the most extreme cases are seen, the problem appears simple and uniform, but if there is opportunity to observe cretins by the dozen and hundreds, ranging in degree from creatures below the level of animals up to somewhat simple citizens who are able to vote, and involving all the variations between dwarfism and normal growth, then the problem appears extremely complicated, and one is inclined to ask what is the common denominator for all of these conditions. This is also true for mongolism. As long as a physician is familiar with only a few marked cases and the literature is based on the study of a few case reports, the problem appears simple. The statement may be heard that mongolism is present or is not present and intermediary stages are unknown. Those, however, who have had the opportunity to study mongoloid persons by the hundreds, and autopsies by the dozens, will agree that mongolism is as variable as cretinism, and all shades of this condition may be observed from the most extreme developmental disorder with idiocy, spinal dysraphism, heart defects, syndactyly, and congenital cataracts, to a borderline condition with an I. Q. of 50. It is my conviction that what has been done in one or two generations for the improvement of cretinism may also be done and is possible for mongolism.

SUMMARY

1. The endocrine aspects of mongolism encompass two separate problems which are frequently confused; mongolism as a prenatal developmental disorder cannot be caused by an endocrine disorder of the mongoloid baby. Mongolism is due either to noxious factors within the mother (endocrine disorder of the mother) or to a genetic inferiority of the germ plasm. The second problem is concerned with the pathology of postnatal development. Is this the result of an abnormal constitution of the child or a dysfunction of its endocrine system? The present study deals with this aspect only.

2. Persons with mongolism show a number of features indicating an endocrine disorder, in contrast to the physical development in other types of mental deficiency. The symptoms of mongolism include,

among others: *a*) Retardation of bone growth, while the time of appearance of ossification centers is about normal. The result is stunted growth or dwarfism and acromicria. *b*) Pathology of gonadal development with lack of sex differentiation, lack of development of secondary sex characteristics and sexual immaturity. *c*) General infantilism with tendency to obesity or general cachexia. *d*) Infantilism of the vascular system.

3. An analysis of the material of 38 autopsies provides the following evidence: *a*) The gonads of mongoloid babies were normal, but those of mongoloid children and adults were immature and showed degeneration. *b*) Adrenal medula and cortex were normal shortly after birth, but in older cases, the cortex had failed to develop normally and remained small. The two outer layers were especially involved; the zona fasciculata was narrow and without the usual lipoid content. *c*) The thyroid was hypoplastic in all cases. The two seeming exceptions (*case 21* and *22*, table 2) had a lymphadenoid goiter and a colloid goiter, respectively. Microscopic examination of the thyroid after birth revealed large areas of microfollicular parenchyma without colloid and irregular fibrosis. After about 7 months of life, the most common picture was a hypoplastic colloid goiter. In 13 instances the colloid goiter was macrofollicular. In 16 instances, there were macrofollicular areas with much colloid besides microfollicular areas with little or no colloid. *d*) The pituitary in mongolism showed a strong tendency to an increase of eosinophilic cells of the anterior lobe. Fifteen cases showed predominance of alpha cells. In 4 cases, beta cells were present besides alpha cells, most of the beta cells being castration cells. In 10 instances, the pituitary showed predominantly chromophobic elements, with frequent necrosis and little or no formation of chromophilic elements. In 3 instances, the pituitary appeared not unusual. The pituitary of the female mongoloid showed a tendency to accumulate brittle colloid, which fills and frequently distends the whole cleft with resulting compresson of the anterior lobe. In contrast to the pituitary of the female, colloid was absent in the pituitary of the male with the exception of one case.

4. These observations explain why previous investigators, whose conclusions were based for the most part on a few case reports, have arrived at contradictory conclusions. A survey of the whole of our own material, as well as that reported in the literature, shows a surprising uniformity of observations, if age and sex of patients are given due consideration.

5. The material at hand furnished conclusive evidence that mongolism is not associated with a primary congenital pathology of the adrenal, but is associated with a secondary pathology of the adrenal cortex, consisting of hypoplasia of the outer layers and lack of lipoid formation. It is suggested that this functional pathology is due to a lack of stimulation by the corticotropic hormone of the pituitary.

6. The material presented provides evidence that mongolism is not associated with a primary congenital pathology of the male and female gonads, but is associated with secondary atrophy and immaturity. It is suggested that the pathology of the gonads is due to the lack of gonadotropic factors from the pituitary and from those glands which influence the gonadal development (adrenal cortex and thyroid).

7. The material presented provides evidence that mongolism is usually not associated with a primary deficiency of the thyroid as is seen in cretinism, but is definitely associated with thyroid pathology. The thyroid is hypoplastic and is more or less a 'resting' colloid goiter. In contrast to the thyroid of cretinism with its inability to produce and store colloid, the thyroid of the mongoloid has this ability, but is inactive because of lack of stimulation. On the basis of the experimental evidence in the literature, it is suggested that the thyroid of the mongoloid is a 'resting' thyroid due to lack of stimulation by the thyrotropic hormone of the pituitary. In the literature on mongolism, the same types of pathology herein reported have been observed—the hypoplastic, degenerated thyroid, and the colloid thyroid with controversial signs of hyperactivity. On the basis of the material now available, it is safe to state that the thyroid of the mongoloid is hypoplastic and hypofunctioning. Although the colloid storage is sufficient to maintain metabolism at a level of about 80 per cent of the normal and 'short of myxedema,' there are indications that the inactivity of the mongoloid thyroid plays an important part in the pathology of mongolism.

8. It is demonstrated that the pituitary of the mongoloid manifests signs of a functional disorder.

9. The material presented seems to permit the conclusion that the developmental disorder of mongolism after birth is not the result of a pathologic constitution (a 'mutation'), but is the result of an endocrine disorder of the pituitary body with ensuing functional pathology of the thyroid, adrenals and gonads.

10. Prevention of mongolism will always remain the main goal. It is, therefore, important to develop means of detecting threatening mongolism during prenatal care. At birth, the mongoloid child is essentially immature. Sometimes there are developmental anomalies which are not amendable to therapy. In less severe cases the main requirement for treatment is to start before edema of the brain, as well as inadequate metabolism of the brain tissue, have produced irreversible changes. In endocrine therapy the complicated character of the pituitary dysfunction has to be

considered, as well as the tendency of the thyroid to colloid goiter, which is in contrast to the hypothyroidism of myxedema and cretinism. Therapy with the preparations now known is not feasible, but it may be hoped that materials soon will be available the use of which will permit a more encouraging view of the whole problem.

I am deeply indebted to Dr. C. Stanley Raymond, Superintendent of the School, for his interest and unceasing support of our research in mongolism; and to my collaborators in the Wallace Research Laboratory.

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EDITORIAL

Suppression of Endocrine Activity by Immunization

THE SUBJECT of antihormones periodically seems to stimulate thought and experimental work directed toward the control of endocrine activity. The practical incentive for much of this work is the relative ease with which hormonal deficiency may be treated by substitution therapy, as contrasted with the complex difficulties often encountered in combating hormonal excess. How may one depress the net activity of an endocrine gland by simple procedures? In a recent issue of ENDOCRINOLOGY there appeared a paper by Jacob Lerman entitled 'Hormone Action of Thyroglobulin Antibodies'[1] which presents interesting data on this problem and raises several important questions.

The experiments described by Lerman embody two outstanding findings. The first of these is that repeated intraperitoneal injection of human thyroglobulin into a rabbit frequently renders the animal hypothyroid or even myxedematous. The second is that such an animal usually shows a poor response to subsequent injections of thyroglobulin intraperitoneally. These are provocative facts which merit further extension of the work and analysis.

Are the antibodies so produced strictly "antihormonic" or rather "anti-protein"? The significance of this distinction is illustrated by a recent report of Francis C. Lowell. He has shown that a patient, both allergic and resistant to crystalline insulin derived from pork and beef pancreas, was allergic but not resistant to human insulin. In this instance it was demonstrated that the patient's serum contained antibodies which physiologically neutralized animal insulin but not human insulin. In other words, the antibodies were "anti-protein" but not necessarily "antihormonic." Similarly Lerman has found that the serum of his immunized rabbits gives a precipitin reaction against a preparation of thyroglobulin (from endemic goiter) which is physiologically inert. Furthermore, thyroglobulin is completely effective when ingested by the immunized animals, which also respond satisfactorily to injected thyroxine.

Therefore, it is not clear how useful such an antiserum might be in combating an excess of thyroid hormone which is already circulating. In Graves' disease, however, in which the source of the hyperthyroidism is endogenous (in the patient's gland), protein-specific antibodies might provide a useful means of suppressing glandular activity on a chemical basis. Such, indeed, is the effect of iodine therapy; but iodine usually is reliable as a practical treatment only for temporary suppression of the thyroid's output of hormone. If carrier-specific antibodies invariably would suppress glandular activity for prolonged periods, a new era in the treatment of endocrine hyperactivity would dawn.

Evidence has been accumulating that endocrine glands may be influenced chemically with resulting decrease in function. To cite one instance, Morgan and Ivy treated 6 young rabbits with intraperitoneal injections of an antiserum prepared by injecting hens with a saline extract of rabbit thyroid. In large doses (10 cc.) the serum was lethal. In smaller doses, however, the animals became 'pot-bellied' and apathetic. The hair was lusterless and shaggy. The animals grew very slowly, and some of them died within 3 months. In such cases the thyroids were so small as to be difficult to find at autopsy. These findings, combined with Lerman's determinations of basal metabolic rate, make a good case for the artificial production of myxedema. There are, furthermore, scattered references in the literature which suggest that other endocrine organs may react similarly.

The mechanism at work in the experiments cited is by no means clear. Is it a direct effect upon the thyroid cells, —perhaps that of a cytolysin? Is the pituitary thryotropic hormone involved? Does the effect bear any relation to the abrupt although temporary fall in basal metabolism commonly encountered clinically when prolonged heavy dosage of thyroid is suddenly interrupted? Why does the immunized animal fail to respond to injected thyroglobulin if he responds readily to thyroglobulin by mouth and to thyroxine obtained from hydrolyzed thyroglobulin? These are points which require investigation.

It should be pointed out that any attempts at application of these results in the clinic must be made with great caution. Intravenous injection of thyroglobulin frequently may lead to allergic exitus. Intramuscular or subcutaneous injections of thyroglobulin may cause abscess formation without much effect on serum antibody titer. Intraperitoneal injections in man raise mechanical objections. Passive immunity, however, as suggested by Rogers and Beebe, may be feasible provided serum reactions can be avoided. Detailed descriptions of this clinical method appeared in 1906 and 1909, and again in 1915, covering its use in some 3000 patients. Fifty per cent of the patients so treated were reported to show striking benefit. Nevertheless, the results tended to be not so dramatic or reliable as the combination of iodine and surgery which, simultaneously developed, has yielded such an enviable statistical record in the past two decades.

On the whole, it may be concluded that immunization or highly purified cytotoxic sera offer an intriguing prospect of suppressing endocrine activity specifically. Further studies in animals are needed before a confident approach to safe clinical application can be envisioned. Nevertheless, the observations thus far are sufficiently stimulating and impressive to justify further investigation, particularly of glands other than the thyroid, for which easy therapeutic control is not available.

W.T.S.

[1] Lerman, J.: Endocrinology 31: 558. 1942.

COMMUNICATIONS TO THE EDITORS

Androgen Therapy in Women

To the Editor:

I have read the letter addressed to you by Dr. E. C. Hamblen,[1] in the September issue (1942) of the Journal of Clinical Endocrinology. He is right in criticizing the abuse of the male hormone, testosterone, in females but one should be careful in condemning the general use of a valuable drug just because some practitioners abuse it. Any potent drug used by one who does not know of its dangers and shortcomings is likely to produce undesirable effects. Dr. Hamblen should condemn the improper use of any new drug by such practitioners, but not the drug itself.

In my experience no other single substance is as desirable as the male hormone to stop lactation when that is necessary. It does away with limitation of fluid intake, with bandaging the breasts and painful engorgement. Three or four injections of 25 mg. will suppress the secretions very thoroughly.

There are female patients who will not respond to estrogenic substances but will respond to the androgens, usually in dosage schedules of 25 mg. 3 times during the first week, twice during the 2nd and once a week thereafter.

There seems to be such a thing as an androgenous mosaic, which Dr. Draper describes,[2] which I am sure other men have also observed. After treating cases of menopausal hyperthyroidism with estrogenic substances, we have found some which did not respond to the female hormone but when androgens were substituted we obtained excellent results; there were no flushes, no tremor; the B.M.R. was lowered and the blood cholesterol was increased.

During the period of 2 or 3 years' observation, a peculiar thing we have observed is that in all of these cases which have reached menopause there was no hirsutism and no change of voice. On the contrary, there is the case of a young unmarried girl who was bleeding excessively; the hemoglobin was very low. She was treated with every drug available; a curettage and a laparotomy were performed. The drug which stopped the bleeding was testosterone, but there was a change in voice and an increase of hirsutes which, however, disappeared a few months later.

I have treated an unmarried woman of 45 who came to me after having been treated with radium for excessive premenopausal bleeding. She was given estrogens and many other drugs but the bleeding and all of the menopausal symptoms persisted. Testosterone was given, with excellent results. She was told beforehand of the possibility of hirsutism and change of voice but neither occurred. At different times, without her knowledge I gave her estrogens. She returned for treatment earlier than usual saying she did not feel so well; she had prolonged bleeding and flushes under the estrogen treatment, while the androgens controlled the symptoms. In none of these menopausal cases did we obtain any masculinizing effects despite the fact that some of the patients were treated for periods as long as 1 to 3 years with the drug.

Gonadotropic hormones have been used in cases in which estrogenic substance should have been used, and vice versa. Potent drugs such as the endocrine preparations should not be used without knowing what is to be expected and the limitations of the therapy.

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[1] Hamblen, E. C.: *J. Clinical Endocrinology* 2: 575. 1942.
[2] Draper, G.: *New England J. Med.* 225: 393. 1941.

An Error in Terminology

To the Editor:

May I raise the question of the heading 'Ovarian Dwarfism' applied by the Editor to our paper 'An Association of short stature, retarded sexual development and high urinary gonadotropin titers in women' in the March, 1942, issue[1] of this Journal. This term is Dr. Albright's and not ours, and it carries a specific connotation which we are not prepared to accept. Indeed, Dr. Albright, if I understand him, has used this term in the spirit of scientific verbal shorthand and has given his own paper on the subject[2] a title nearly as cumbersome as ours. That this heading can readily be regarded as ours is evidenced by Dr. E. K. Shelton's comment on the propriety of the term in his article[3] in the June issue of *Endocrinology*, 1942.

[1] Varney, R. F., A. T. Kenyon and F. C. Koch: An association of short stature, retarded sexual development and high urinary gonadotropin titers in women. *J. Clinical Endocrinology* 2: 137. 1942.

[2] Albright, F., P. H. Smith and R. Fraser: A syndrome characterized by primary ovarian insufficiency and decreased stature. *Tr. Assoc. Am. Phys.* In press. *Am. J. Med. Sc.* In press.

[3] Shelton, E. K.: The clinical aspects of dwarfing. *Endocrinology* 30: 1000. 1942.

We would greatly appreciate the publication of this letter in the current volume of the JOURNAL OF CLINICAL ENDOCRINOLOGY, so that such of your readers as are interested may understand that we deserve neither the credit nor the responsibility for the expression 'ovarian dwarfism.'

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Diagnosis of Simmonds' Disease

TO THE EDITOR:

MAY WE offer a short comment on the reference in the article by Moss,[1] to the use of two tests (urinary 17-ketosteroid excretion and insulin tolerance test) which we have advocated[2] for the diagnosis of Simmonds' disease. The author remarks that he attempted but failed, with his *case 1*, to establish the diagnosis by these two tests. While welcoming his interest in the tests, we submit that the evidence, in his excellent clinical description and postmortem report of this case, is against Simmonds' disease having been present. Chronic malnutrition consequent on the frequent vomiting is surely adequate explanation for the clinical features which had suggested this diagnosis, and the postmortem findings of a relatively normal anterior pituitary serve to bear this out, and confirm the results of the above-mentioned tests. There is probably some lowering of anterior pituitary function in malnutrition, but these tests appear to distinguish the more extensive lowering of function which must occur before primary organic disease of the anterior pituitary produces the symptoms of Simmonds' disease.

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[1] MOSS, R. E.: *J. Clinical Endocrinology* 2: 395. 1942.
[2] FRASER, R., AND P. H. SMITH: *Quart. J. Med.* 10: 297. 1941.

Abstracts of
CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

ADRENALS

HERMANN, O.

Cholesterol content of adrenals of newborn and sucklings. *Monatschr. f. Kinderh.* 82: 76. 1940.

Considerable variations in the amount of free and bound cholesterol were found. In rickets, weight of adrenals as well as their fat and lipin content were greatly increased. Very high values were found in pyoderma and miliary tuberculosis. Cholesterol values were very low in disturbances of nutrition and in a case of congenital syphilis, the weight of the adrenals was decreased. In dystrophias, high cholesterol values were found. In all pathological cases, the adrenal cholesterol values corresponded generally with those of blood.—*Courtesy Chem. Abstracts.*

TALBOTT, J. H., L. J. PECORA, R. S. MELVILLE, AND W. V. CONSOLAZIO.

Renal function in patients with Addison's disease or adrenal insufficiency secondary to pituitary pan-hypofunction. *J. Clin. Invest.* 21: 107. 1942.

The clinical tests for renal disease were normal in most patients. Rate of formation of glomerular filtrate and tubular reabsorptive capacity for glucose were abnormal. Renal plasma flow was affected less and tubular capacity for excreting diodrast least. The filtration fraction was depressed below normal. Administration of desoxycorticosterone acetate corrected partly, but only temporarily, these deficiencies; adrenal cortical extract had no action. Administration of desoxycorticosterone acetate to two normal persons was without effect on renal activity.—*Courtesy Brit. Chem. and Phys. Abstracts.*

THORSTAD, M. J.

Adrenal apoplexy, *Am. J. Surg.* 55: 44. 1942.

Acute adrenal apoplexy must be considered in the differential diagnosis of an acute abdominal condition. A review of the literature since 1928 revealed twenty-two reported cases of this disease. Two additional cases of unilateral adrenal apoplexy in the adult are presented.

Suprarenal hemorrhage may occur unilaterally or bilaterally, the latter being the more common, there being marked variations in the extent of the hemorrhage from scattered areas with little destruction of the parenchyma to conversion of the entire gland into a blood sac. The disease may be characterized by acute abdominal symptoms by general asthenia or by delirium, convulsions and coma. There are no pathognomonic signs or symptoms and a diagnosis is difficult to make. Treatment is largely supportive supplemented by the surgical removal of the adrenal in unilateral apoplexy.—*Author's summary.*

ENDOCRINE GENERAL

ASCHHEIM, S.

Simplified method for biological diagnosis of pregnancy. *J. Lab. clin. Med.*, 27: 547, 1942.

Two female immature rats, 4–5 weeks old, receive 1 subcutaneous injection of 0.5 cc. of the urine. Vaginal smears of both rats are made 72–84 and 96 hrs. after. In pregnancy, only epithelial cells without free mucus or leucocytes are found in the vagina after 72 (often 66) hours. After 84–96 hours keratinized cells (seldom mixed with a few epithelial cells) are found which are the criterion of a positive reaction.—*D.A.M.*

BRONSTEIN, I. P., J. A. LUHAN AND W. B. MAVRELIS.

Sexual precocity associated with hyperplastic abnormality of the tuber cinereum. *Am. J. Dis. Child.* 64: 211, 1942.

A case of sexual precocity in a twenty-two month old girl is reported adding another to the 17 cases of precocious puberty and hypothalamic tumors collected by Weinberg and Grant in 1941. Death occurred through an accidental meningitis and necropsy revealed a small tumor-like mass beneath the floor of the third ventricle, between the infundibulum and the mamillary bodies. The structure of this hyperplastic malformation was not unlike that of the tuber cinereum. There was a relative eosinophilic hyperplasia of the pars distalis of the hypophysis.—*M.B.G.*

BROWN, W. E.

Treatment of gonorrheal vulvovaginitis with estrogens. *Am. J. Dis. Child.* 64: 220, 1942.

Persistent cornification of the vaginal epithelium is necessary for cure of gonorrheal vulvovaginitis and its absence is responsible for many of the reported failures with estrogens. The author reports bacteriological and clinical cures in 19 cases in girls, 13 of which were gonococcic and 6 non-specific in origin. Sulfanilamide or derivatives were unsuccessful. No complications were encountered.—*M.B.G.*

DOBRINER, K., E. GORDON, C. P., RHOADS, S. LIEBERMAN AND L. F. FIESER.

Steroid hormone excretion by normal and pathological individuals. *Science* 95: 534. 1942.

Urine was collected over a 6 month period from 6 normal persons, 6 patients with cancer, one with cancer of the adrenals and 4 with clinical evidence of adrenal hyperplasia. After hydrolysis, urine was fractionated into acidic, phenolic and neutral fractions. Neutral fractions were separated into ketonic and non-ketonic fractions, each of these being further separated with digitonin into 3-alpha and 3-beta-ketosteroids. Excretion of total ketosteroids, 10–20 mg. per day in normal persons, 5–10 mg. in cancer patients, 40–60 mg. in adrenal hyperplasia and 285 mg. in the patient with adrenal cancer. Of the total ketosteroids, the percent excretion of beta-ketosteroid was 0.6–2.2 in normals, 0.3–6.0 in cancer patients, 3.7–11.4 in adrenal hyperplasia, and 66.0 in the patient with adrenal cancer. Further fractionation of alpha-ketosteroid fractions yielded androsterone-17, androsterone, 3α-hydroetiocholan-17-one and 4 unidentified steroids as well as impure substances. Proportions in all patients and in normal subjects are presented.—*D.A.M.*

EVANS, H. M. AND A. GORBMAN.

Urinary gonadotropins in normal men. *Proc. Soc. Exper. Biol. & Med.* 49: 674. 1942.

A modified alcohol precipitation method is described for preparation of non-toxic gonadotropic concentrates from normal male urine. Assayed in female immature rats, such concentrates of pooled samples of urine from healthy college men gave titers of 1.0 to 4.5 rat units per liter. In normal female mice the titers were 6 to 20 mouse units per liter. Assayed in hypophysectomized rats, the concentrates produce follicle stimulation and interstitial cell repair at the same dosage level, although in some cases, follicle stimulation may be produced at dosage levels as low as one-third that required for interstitial cell repair.—*Courtesy Chem. Abstracts.*

FOSS, G. L.

Implantation of sex hormone tablets in man. *J. Endocrinol.* 3: 107, 1942.

Weighed tablets made from compressed crystals of estrone, estradiol, testosterone propionate, testosterone and progesterone were implanted in male and female patients subcutaneously. At varying periods of time, these were removed and weighed. The average rate of absorption increased in the order given, tissue reactions varying directly with the rate of absorption.—*Courtesy Chem. Abstracts.*

DIAZ MINDURRY, EUGENIO F.

Cardiac neurosis and endocrine function. *Semana méd.* 49: 1159. 1942.

Complaint of patients of palpitations, arrhythmias and precordial pain with or without irradiations is often accompanied only by insignificant objective findings such as extrasystoles, tachycardia, while heart sounds, blood pressure, electrocardiogram and X ray examination reveal nothing unusual. The striking feature is a peculiar psychic disturbance that either precedes the heart symptoms and induces their appearance following constant self-observation or finds its origin in primary minor heart irregularities. The malicious circle that follows develops often on an endocrine basis. Hyperfunction of the thyroid may be the determining factor without any of the typical symptoms of Graves' disease. The metabolic rate is the most important diagnostic help in these cases. Treatment consists in avoidance of all psychic and chemical stimulation (coffee, alcohol, etc.) administration of diiodotyrosine in series of 20 days' treatment, and insulin, 10 to 20 units 30 minutes before breakfast with or without the addition of carbohydrates. Adrenocortical deficiency is difficult to diagnose. It is characterized by asthenia, loss of weight and often by enteroptosis. The blood sugar is subnormal and the response to 10 units of insulin is enhanced. The ascorbic acid and cholesterol in the blood are low but K and Na are not sufficiently affected to be of diagnostic value. Treatment with desoxycorticosterone is valuable. In the menopausal estrogen deficiency parenteral doses of 1 to 5 mg of estrogen 1 to 3 times weekly may be given or 10,000 units several times daily orally. In the premenopausal deficiency the doses should not exceed 500 to 1,000 units daily to avoid metrorrhagias.—*A.E.M.*

NATHANSON, I. T.

Treatment of mammary pain and secretion with testosterone propionate. *New Eng. Jour. Med.* 226: 323. 1942.

Testosterone propionate was administered to 30 carefully selected patients with severe mammary pain and secretion. Relief occurred in a high percentage of the cases, effectiveness of this treatment being definitely better than with estrogens. Recurrence of symptoms is a rule usually within 6 months after discontinuence of treatment. Prolonged and continuous treatment is not recommended and care must be exercised in selection of cases presenting psychogenic elements.—*D.A.M.*

RABINOW, M.

Appearance of ossification centers. Groupings obtained from factor analysis. *Am. J. Dis. Child.* 64: 229, 1942.

The ages were determined at which certain centers of ossification appeared in a group of 31 children. These data were interrelated and subjected to factor analysis. The analysis yielded three factors, a "round bone" factor, an "epiphysis" factor and a third factor which was possibly an artefact. The author suggests that bone development be expressed on the basis of "round bone skeletal age" and "epiphysis skeletal age." It is possible for the carpals and tarsals to be normal in time of appearance and maturation and for the epiphysis to be retarded and vice-versa.—*M.B.G.*

RANDALL, L. M. AND M. H. POWER.

Amounts of glycogen in endometrium. *Proc. Staff Meet., Mayo Clin.* 17: 158. 1942.

Glycogen concentration of endometrial tissues vary with the different phases of the menstrual cycle. Four specimens showing only proliferative phase on microscopic examinations showed an average of 0.171 per cent glycogen. Three specimens from late proliferative and early differentiative phases of the endometrium contained an average of .35 per cent glycogen. Six specimens from early differentiative phase averaged 1.09 per cent glycogen. Seventeen specimens in the late differentiative phase contained .71 per cent glycogen.—*D.A.M.*

ROBINSON, M.

Investigation of breast feeding; a study of 1,000 mothers. *Arch. Dis. Childhood*, 17: 23. 1942.

Breast-feeding is not affected by the following: season of the year, parity or the age of the mother, size of the breasts, antenatal presence of secretion in the breasts, return of menstruation, rheumatic endocarditis, simple enlargement of the thyroid, pre-eclampsia, and antenatal symptoms relieved by Ca. Breast-feeding is affected by the size and character of the nipple, masculinity, obesity, morning sickness, pyelitis, severe varicose veins, breast abscesses and cracked nipple. 52% of early weaning occurs in all types before the end of the first month.—*Courtesy Brit. Chem. and Phys. Abstracts.*

STURGIS, S. H.

The use of stilbestrol in the relief of essential dysmenorrhea. *New England J. Med.* 226: 371. 1942.

Daily doses of 1 mg. diethylstilbestrol is given orally for a period of 20 days beginning at least three weeks before the expected onset of menstruation as recorded from a number of previous menstrual cycles. This therapy primarily inhibits the follicle stimulating hormone of the pituitary and secondarily suppresses growth of ovarian follicles and ovulation. After discontinuance of treatment, normal cycles are re-established with the invariable recurrence in about one month of typical dysmenorrhea. In 20 per cent of patients, treatment must be discontinued because of gastrointestinal complaints. Estrogen therapy for essential dysmenorrhea is of value as a temporary rather than permanent form of relief.—*D.A.M.*

TIEN, D. S. P.

Significance of pregnanediol in pregnancy urine. *Chinese M. J.* 59: 416. 1941.

Excretion of pregnanediol by Chinese women at various stages of gestation corresponds with that described in Western women. It is premature to regard excretion of pregnanediol as an accurate index of corpus luteum activity. In twin pregnancy, pregnanediol excretion was abnormally high throughout. Isobutyl alcohol is inferior to normal butyl alcohol as an extraction solvent.—*Courtesy Chem. Abstracts.*

GONADS

BELL, G. H.

The behavior of the uterus of the rhesus monkey under the influence of certain hormones. *J. Endocrinol.* 3: 87. 1942.

Effects of various hormones on uterine movements of ovariectomized animals were recorded. Animals received estrone in oil, estrone followed by testosterone and estrone followed by progesterone. Spontaneous reactivity, in vivo, and reactivity due to oxytocin injections were variable in all groups and in untreated controls and showed practically no difference between groups except that contraction waves were low in the estrone-testosterone group and somewhat slower in the estrone-progesterone treated group. Vasopressin produced relaxation in all groups. Comparison of these results with the recorded behavior of the human uterus is discussed.—*D.A.M.*

BYRNE, W. H., J. C. WEED, B. B. WEINSTEIN AND C. G. COLLINS.

Vitamins and stillboestral in treatment of hypo-ovarianism. *New Orleans Med. J.* 94: 330. 1942.

Report of 57 cases with menopausal symptoms. The addition of a combined vitamin preparation did not lessen the incidence of nausea.—*Courtesy Brit. Chem. and Phys. Abstracts.*

FERRIS, D. O.

Pathology of tumors of the testis: correlation with excretion of hormone in the urine. *Proc. Staff Meet., Mayo Clin.* 16: 615. 1941.

Increased amounts of urinary gonadotropin are found in all cases of malignant tumors of the testis. Using the method of Frank (1935), the author finds that values below 20 rat units per liter may be considered nonpathologic whereas those above this value are presumptive of pathology.—*D.A.M.*

HECKEL, N. J. AND H. L. KRETSCHMER.

Carcinoma of the prostate treated with diethylstilbestrol. *J.A.M.A.* 119: 1087. 1942.

The carcinoma of the prostate softened under diethylstilbestrol treatment—3 to 12 mgm. daily. The patient gained weight and the subjective symptoms disappeared. Histologically the neoplastic cells showed hydropic degeneration and vacuolization.—*C.C.P.*

WEINHOUSE, G. AND J. I. BREWER.

Cyclic variations in the lipids of the corpus luteum. *J. Biol. Chem.* 143: 617. 1942.

Free cholesterol remains relatively constant throughout all stages of development of the human corpus luteum. Cholesterol esters remain constant or decline slightly with increasing activity, reaching lowest values in actively functioning corpus luteum of pregnancy. In the regressive phase, cholesterol esters increase to five times their value during functional periods. Phospholipids increase gradually with age of the organ reaching maximal values during

maximal function. They decline slightly during regression. Glycerides do not vary appreciably during development of the corpus luteum but large increases occur during regression. Cyclic changes in phospholipids are not accompanied by significant changes in relative proportions of lecithin, cephalin or sphingomyelin.—*Courtesy Chem. Abstracts.*

HYPOPHYSIS

JEFFERS, WM. A., MARY M. LIVEZEY AND J. H. AUSTIN.

A method for demonstrating an antidiuretic action of minute amounts of pitressin. Statistical analysis of results. *Proc. Soc. Exper. Biol. and Med.* 50: 184, 1942.

Rats are made diuretic by giving water by stomach tube, the water containing sufficient alcohol to produce mild sedation. 20 microunits (0.00002 units) given intravenous produce detectable antidiuretic effects.—*D.A.M.*

PANCREAS

BARNARD, R. D.

Insulin ferrihemochromogen. *J. Lab. & Clin. Med.* 27: 774. 1942.

Insulin combines with ferriheme (hematin) in anhydrous ammonia forming various insulin-ferriheme conjugates depending on the proportions of reacting components. These ferrihemochromogen compounds are water soluble and are physiologically active; those of the lower insulin to ferriheme ratios showing a prolonged and delayed action similar to that produced by depot forms of insulin. No clinical data are presented.—*Author's abstract.*

BERG, MAX.

Absorption of intracutaneously injected solutions of dextrose and sodium chloride. Comparison of absorption time for diabetic and non-diabetic subjects. *Arch. Int. Med.* 69: 99. 1942.

In 173 observations on 3 groups, persons with uncontrolled diabetes, persons with controlled diabetes and on non-diabetic subjects, absorption rates of intracutaneous injections of various solutions including .85% saline, 0.1% and 5.0% glucose and 1.7% urea, were studied.

Despite relatively wide ranges of fluctuations in actual absorption times for individual tests, definite differences were observed between the ratio of absorption times of various solutions of glucose to the absorption time of saline for persons with uncontrolled diabetes and for persons with controlled diabetes. The latter ratio was similar to that of normal subjects.

Differences could not be explained by states of hydration but were related more directly to permeability of skin.—*D.A.M.*

COLWELL, A. R., J. L. IZZO, AND W. A. STRYKER.

Intermediate action of mixtures of soluble insulin and protamine zinc insulin. *Arch. Int. Med.* 69: 931. 1942.

1. Suitable mixtures of the 2 standard insulins may be prepared which show any desired intermediate action between the 2 in promptness, intensity and duration of effect. 2. Such intermediate effects gain intensity and promptness at the expense of prolongation of action. The converse is also true. 3. Intermediate effects which are decisive cannot be obtained with simple mixtures of the 2 insulins until as much soluble insulin as protamine zinc insulin is used in them. 4. Probably mixtures containing more regular insulin than protamine zinc insulin, possibly 2 or 3 times as much, are most suitable for daily use in the treatment of severe diabetes. 5. Such mixtures owe their intermediate effects to reduction in the amount of protamine, zinc or alkaline buffer. There is evidence to indicate that insulin in a different physical or chemical form is responsible for the modified action rather than composite effects from simple fractions of soluble insulin and insoluble protamine ainc insulin. 6. Results of treatment with these modifications suggest that better control of severe diabetes mellitus may be obtained with single daily doses of 1 of them than with protamine zinc insulin or unmodified insulin given alone or both administered simultaneously in separate doses. Multiple injections may be avoided and dosage reduced because of greater efficiency.—*I.B.*

GLASS, W. L., C. L. SPINGARN, AND H. POLLACK.

Unusually high insulin requirements in diabetes mellitus. Report of a case. *Arch. Int. Med.* 70: 221. 1942.

A case is described of diabetes mellitus in which the insulin requirement was more than 85,000 units of insulin in a 5½ month period of observation. During episodes of ketotic acidosis it was necessary to give 2,360 units, 2,500 units and 2,795 units of insulin in 24 hours before adequate control was accomplished. No definite cause for the insulin-refractory state could be determined. Therapeutic procedures included roentgen irradiation over the pituitary and the administration of lipocaic. It was not possible to establish a definite relation between these forms of therapy and the improvement which followed their use. The excessive insulin need subsided 6 months after its onset, and the patient remained mildly diabetic for the subsequent 6 months.—*I.B.*

JOSLIN, E. P., H. F. ROOT, P. WHITE AND A. MARBLE

Diabetic coma. *J.A.M.A.* 119: 1160. 1942.

In the past two years 62 consecutive cases of diabetic coma were successfully treated by prompt and energetic use of large doses (200 units in 2 hours) of insulin. Supportive measures were: (1) Adequate saline therapy to overcome dehydration, (2) Routine gastric lavage to relieve persistent distention, and (3) Constant intravenous infusion of fluid, plasma or blood to restore blood volume and support the circulation. No dextrose or alkali was used. Previous to the institution of the above therapeutic regime the mortality had been 11%.—*C.C.P.*

KERWIN, A. J.

Fatal hyperinsulinism with cerebral lesions due to pancreatic adenoma. *Am. J. Med. Sci.* 203: 363. 1942.

A case of fatal hyperinsulinism due to multiple islet cell-tumors of the pancreas is reported. The patient died 16 days after the onset of the first symptoms, and after 8 days of continuous coma. The tumor contained 30 units

of insulin per g. of tissue. The brain showed congestion, edema, hemorrhages, nerve cell degeneration, and gliosis, but these changes were not severe.—*Courtesy British Chemical and Physiological Abstracts.*

LOZINSKI, E. AND L. I. FROHLICH

Resistance to insulin. *Canad. M. A. J.* 46: 62. 1942.

A case of resistance to insulin is described in whom 3000–4000 units of insulin daily were required to prevent hyperglycemia, acidosis, and coma. There was no evidence of the presence of an anti-insulin or insulin-destroying substance in the patient's serum or of insulin excretion in the urine. Irradiation of the pituitary gave a satisfactory response.—*Courtesy British Chemical and Physiological Abstracts.*

PARATHYROID

ANDERSON, G. W. AND L. MUSSELMAN.

Treatment of tetany in pregnancy with a brief review of literature. *Am. J. Obst. & Gynec.* 43: 547. 1942.

A review of 240 reported cases of tetany in pregnancy is presented. These were classified in 4 types: 26 were of the postoperative hypoparathyroid type of tetany with pregnancy; 145 were of the idiopathic or spontaneous type including those occuring during pregnancy, in labor or post partum. A third group of 9 cases due to low Ca intake and vitamin D deficiency is reviewed. The last group included 60 cases associated with thyroid deficiency disease. Relationships of tetany to menstruation, lactation, blood loss at delivery, hyperventilation and low Ca intake is discussed. Past and modern treatment is reviewed. The latter consists of oral and intravenous Ca, parathyroid hormone and dihydrotachysterol. Of 3 cases of the postoperative type treated by the author, two went to successful term. Therapeutic abortion was necessary in one because of pre-eclamptic toxemia.—*Author's abstract.*

HARDING, F. E.

Use of dihydrotachysterol in parathyroprivic tetany. *J. Lab. Clin. Med.* 27: 497. 1942.

Treatment of a case of parathyroprivic tetany with injury to the recurrent laryngeal nerve is described. The nerve regenerated in a few months, but deficiency in parathyroid hormone continued after 1½ years. Maximal improvement occurred with intensive treatment with low P diet, Ca gluconate, irradiated ergosterol, dihydrotachysterol and thyroid extract. Dihydrotachysterol (1 cc. daily) raised the blood Ca, prevented tetany and partly decreased laryngeal stridor. Thyroid extract raised the B.M.R. and further improved the laryngeal stridor.—*Courtesy Brit. Chem. and Physiol. Abstracts.*

WOO, T. T., C. FAN AND F. T. CHU.

Treatment of infantile tetany with dihydrotachysterol. *Chinese M. J.* 60: 99. 1941.

Serum Ca was restored to normal levels and tetany relieved in 4 of 5 infants by A.T. 10 in daily doses of 1.0 to 1.5 cc. for 1 to 4 days. The resistant case, which had a very low serum Ca, responded to vitamin D.—*Courtesy Brit. Chem. and Physiol. Abstracts.*

THYROID

BREIDENBACH, L. AND E. APPELBAUM

Masked hyperthyroidism. *Ann. Surg.* 115: 184. 1942.

Great emphasis was laid on the importance of bearing in mind the possibility of thyrotoxicosis when a patient presents an atypical clinical picture of some other type of disease, particularly organic heart disease, with or without congestive heart failure, angina pectoris or auricular fibrillation, diabetes mellitus, hypertension, some form of gastro-intestinal disturbance, or a psychoneurosis.

Diagnosis of masked hyperthyroidism, in addition to the points mentioned, is based on certain suggestive signs and symptoms as persistent moderate tachycardia, unexplained weight loss, an increase in the basal metabolic rate, improvement or relief of symptoms, decrease in the basal metabolic rate following iodine medication and thyroidectomy, and, finally, the histologic report of the removed gland.—*Authors' summary.*

HERTZ, A. AND A. ROBERTS.

Use of radioactive iodine in differential diagnosis of two types of Graves' disease. *J. Clin. Invest.* 21: 31. 1942.

The ophthalmopathic type of Graves' disease patient excretes more I from a 2 mg. (or less) test dose and takes up less in the thyroid than the classic Graves' disease patient. The urinary I excretion can be used as a diagnostic aid in distinguishing the two types of patients.—*Courtesy Brit. Chem. and Phys. Abstracts.*

HERTZ, S., A. ROBERTS AND W. T. SALTER.

Metabolism of iodine in Graves' disease. *J. Clin. Invest.* 21: 25. 1942.

In 22 thyrotoxic patients and 2 normal persons, urinary excretion, thyroid uptake and retention, and chemical distribution of the thyroid-I were studied using radioactive I. The largest percentage uptakes in the thyroid were at low dosage levels of I. Pre-iodinization decreased subsequent thyroid-I uptake. The hyperplastic thyroid of Graves' disease may take up 80 per cent or more from a sufficiently small dose (2 mg.); urinary excretion accounts for most of the remainder. Analysis of the thyroid after operation for thyroxine-like and non-thyroxine-like fractions showed the labelled I to be increasingly in the former fraction as the time following administration increases.—*Courtesy Brit. Chem. and Physiol. Abstracts.*

HEYD, C. G.

Mortality and morbidity in surgery of the thyroid. *Am. J. Surg.* 60: 18. 1942.

In a series of 652 resections of the thyroid for all surgical conditions there were eighteen deaths or an overall mortality of 2.7 per cent: of these fifteen were carcinomata with three deaths.

Graves' disease contributed 44 per cent of the material; toxic adenomas 16 per cent; nontoxic adenomas 36 per cent; thyroiditis, including Riedel's struma, 1.5 per cent, and malignancy 2.3 per cent. The contrast between Graves' disease and toxic adenomas is marked in many details. The average age of this latter group was forty-four years as against thirty-four years for the Graves' disease group, and less than 5 per cent had eye signs. Furthermore, the average basal metabolism was +31 for toxic adenomas as contrasted with +46 in the Graves' disease group.

Approximately 3% of the cases of Graves' disease had a recurrence of hyperthyroidism and approximately 3% came from other clinics, making an overall of recurrent hyperthyroidisms of 6%.

Approximately 50 per cent of the cases of toxic adenomas have cardiac symptoms and at least half of these have definite organic heart disease. The degree of heart impairment is directly proportional to the chronicity of the hyperthyroidism and some of the most brilliant results in thyroid surgery are obtained in the patients with thyrotoxic heart conditions from toxic adenomas. The operative risk in this group of patients is great; but if a patient with a thyrotoxic heart is able to be on his feet and walk about, he is usually able to survive a thyroid resection after adequate preoperative treatment and rest in bed.—*Author's summary.*

Preston, F. W. and W. O. Thompson.

Persistence and recurrence of toxic goiter following subtotal thyroidectomy. *Arch. Int. Med.* 69: 1019. 1942.

Of 294 patients with toxic goiter undergoing subtotal thyroidectomies during the period 1930 to 1939 and followed up from 3 months to 10 years after operation, 39 showed definite clinical evidence of postoperative thyrotoxicosis. Of this number, 37 were among 212 patients with exophthalmic goiter (17.5 per cent) and 2 among 82 patients with toxic adenoma (2.4 per cent). The thyrotoxicosis was usually less severe than before operation, although in 3 patients it was more severe. In 22 of 33 patients on whom the observation was made it was found that postoperative thyrotoxicosis could be adequately controlled with iodine alone. In 11 of these patients who had a persistence of the disease, permanent remission was observed between 4 months and 3 years after operation. There was a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of postoperative thyrotoxicosis, although there were important exceptions to this rule. Thus regeneration of thyroid tissue was observed in 74 per cent of patients with postoperative thyrotoxicosis but in only 15 per cent of those without thyrotoxicosis after operation. Of the patients as a whole, regeneration was observed in 22 per cent. Two main factors are responsible for thyrotoxicosis following subtotal thyroidectomy for toxic goiter: (1) the failure of the operation to remove the cause of the disease, and (2) the removal of too little thyroid tissue. It is probably desirable to reoperate on all patients with postoperative thyrotoxicosis in whom the basal metabolic rate cannot be held at or near the standard normal level (below plus 15 per cent) by the administration of iodine. Postoperative administration of iodine will not prevent the regeneration of thyroid tissue. The course of postoperative thyrotoxicosis, including its tendency toward remissions and relapses, resembles the course of the untreated disease.—*I.B.*

Soley, M. H.

Exophthalmos in patients with various types of goiter. *Arch. Int. Med.* 70: 206. 1942.

According to the studies reported here, the eyes of patients with nontoxic nodular goiter are no more prominent than those of normal persons. Patients with toxic nodular goiter tend to have more prominent eyes than normal persons but not as prominent as patients with toxic diffuse goiter. The eyes of patients with toxic diffuse goiter are significantly more prominent than those of normal persons or of patients with nontoxic nodular goiter. The eyes of over 50 per cent of the patients with toxic diffuse goiter become measurably more prominent after subtotal thyroidectomy; they become less prominent in only a small percentage of persons. These observations are contrary to the opinion of most surgeons who have relied on clinical impressions as to the state of exophthalmos before and after treatment. It is apparent that loss of the stare associated with hyperthyroidism does not necessarily mean a decrease in exophthalmos. The eyes of thyrotoxic patients treated by roentgen rays show less tendency to increase in prominence. It is suggested, therefore, that for patients with hyperthyroidism in whom exophthalmos is severe, roentgen therapy is more desirable than surgical subtotal thyroidectomy. Furthermore, it is advised that the treatment in this particular group be directed toward preventing the occurrence of malignant exophthalmos.—*I.B.*

ASSOCIATION NOTICE

Announcement of the Annual Meeting

The meeting herein announced will be held contingent upon authorization by the Office of Defense Transportation.

THE TWENTY-SEVENTH ANNUAL MEETING of The Association for the Study of Internal Secretions will be held in Cleveland, on Monday and Tuesday, April 5 and 6, 1943. The Hotel Cleveland will be headquarters for registration and for the scientific and business sessions. Room reservations should be made early with the Hotel Cleveland.

The Chairman of the Local Committee is Dr. E. Perry McCullagh, Cleveland Clinic, Cleveland, Ohio.

PRESENTATION OF PAPERS

1. The title of the paper and four copies of a comprehensive abstract must reach the President, Dr. E. Kost Shelton, 921 Westwood Boulevard, Los Angeles, Calif., not later than February 10, 1943.

Abstracts submitted should be in proper form for printing in ENDOCRINOLOGY. Not more than the first 200 words can be included in the printed abstract.

2. Non-members who wish to present papers must have titles and abstracts introduced by members.

3. The abstracts of papers will be considered by the Program Committee and the final program announced about March 10, 1943.

4. Papers will be limited to ten minutes for presentation. A ten-minute presentation is designed for condensed discussion of new investigations, either in laboratory or clinical phases of endocrinology. Previous publication or presentation before other societies of national membership may be cause for omitting a paper from the program.

5. Papers presented at the Annual Meeting may be submitted for publication to the Editor of ENDOCRINOLOGY or the JOURNAL OF CLINICAL ENDOCRINOLOGY. Such submission is invited. Acceptance of a paper for the program does not necessarily mean its acceptance for publication.

You are invited to bring this announcement to the attention of your colleagues and associates who have endocrine research in progress.

NOMINATION OF OFFICERS

The By-Laws of the Association provide that nominations for all elective offices shall be made by a Nominating Committee and forwarded to the Secretary at least sixty days before the annual meeting. The Nominating Committee for the current year, appointed by the President and accepted by the Council, is as follows:

Dr. E. Perry McCullagh, *Chairman*, Cleveland Clinic, Cleveland, Ohio.
Dr. C. N. H. Long, Yale University School of Medicine, New Haven, Connecticut.
Dr. Warren O. Nelson, Department of Anatomy, Wayne University, Detroit, Michigan.

The By-Laws also provide (Article V, Section 2) that "Any member of the Association may submit nominations to the Nominating Committee for its consideration." Nominations may be sent to the Chairman, Dr. E. Perry McCullagh, before Feb. 1, 1943.

The terms of the following officers expire at the time of the Annual Meeting in Cleveland in 1943:

President-Elect	Carl R. Moore
Vice-President	John C. Burch
Secretary-Treasurer	Henry H. Turner

Council Members

P. E. Smith M. A. Goldzieher George W. Thorn

Publication Board

E. C. Hamblen Carl R. Moore

THE E. R. SQUIBB & SONS AWARD

The E. R. Squibb & Sons Award of $1,000.00 was established in 1939, and was given first in 1940 to Dr. G. W. Corner, in 1941 to Dr. Philip E. Smith, and in 1942 to Dr. Fred C. Koch. A special Committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology.

THE CIBA AWARD

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than 35 years of age in the field of endocrinology was established last year, but no recipient was selected due to lack of time. The work cited may be either in the field of pre-clinical or clinical endocrinology. The Award is for $1200.00. If the recipient should choose to use the Award toward further study in a laboratory other than that in which he is at present working, the Award will be increased to $1800.00. The option is left entirely to the recipient.

Each member has the privilege of making one nomination for each Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions in endocrinology and by a bibliography of the nominee's most important publications, and reprints if possible. Five copies should be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, not later than February 1, 1943.

E. Kost Shelton, *President*
Henry H. Turner, *Secretary*

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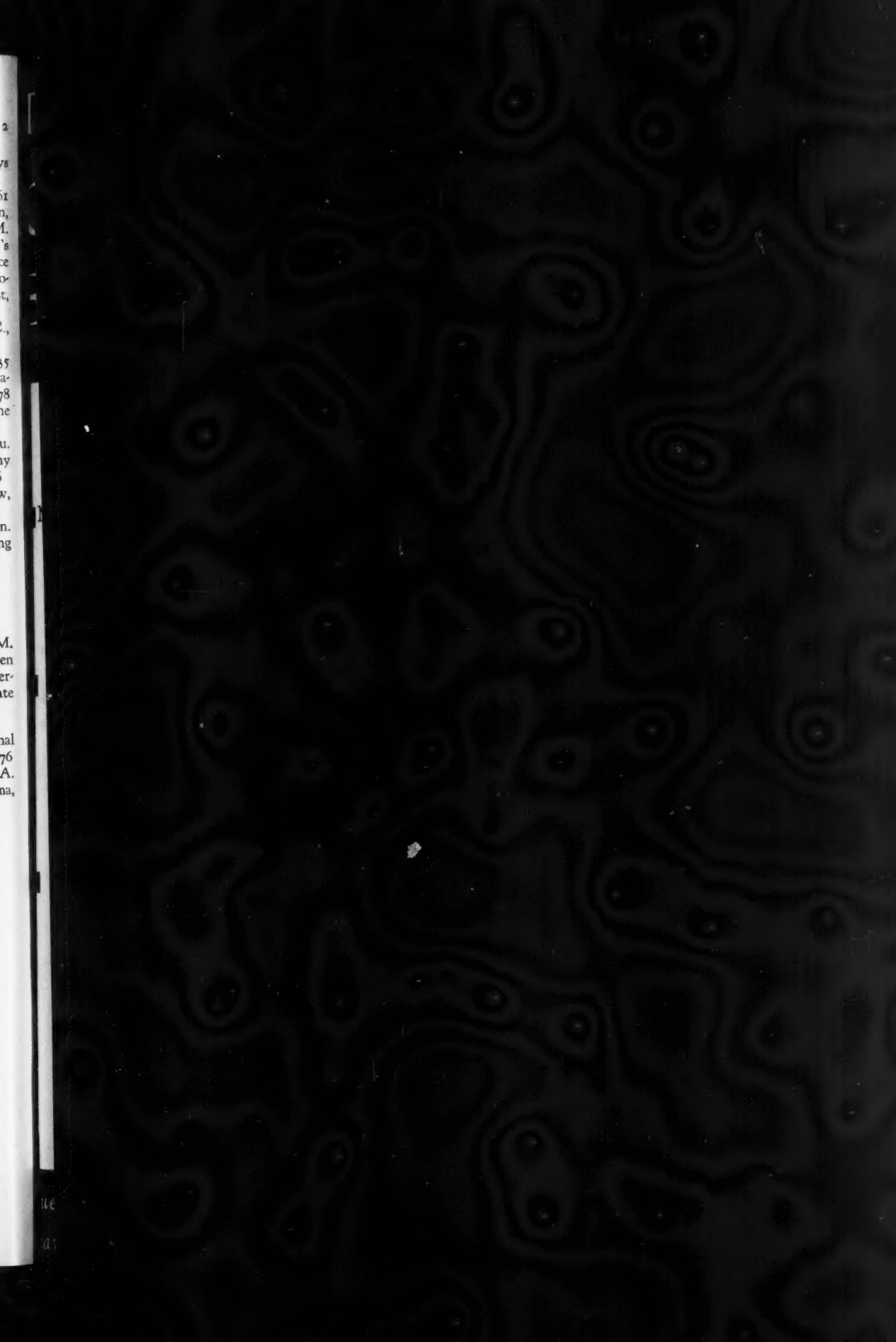

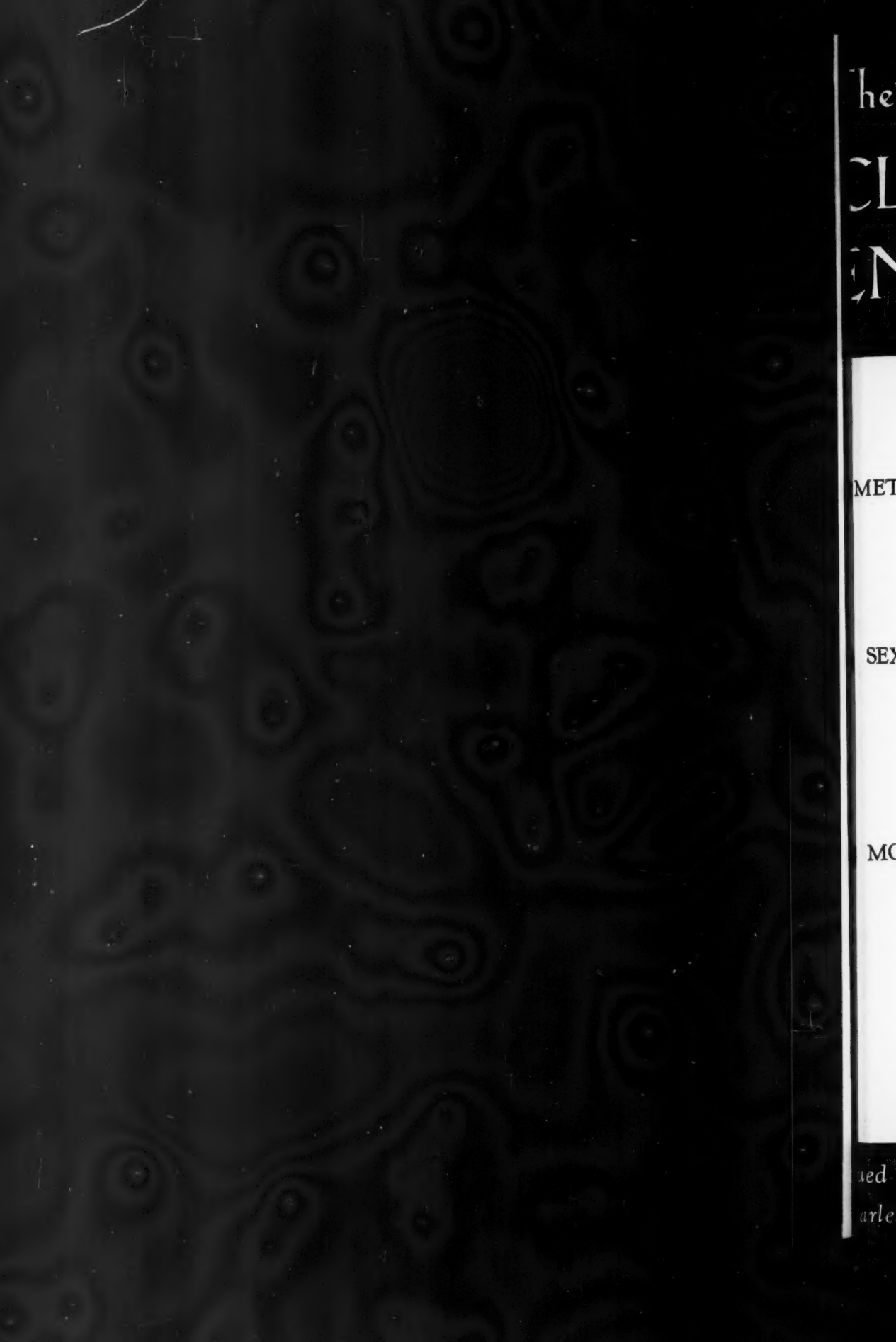
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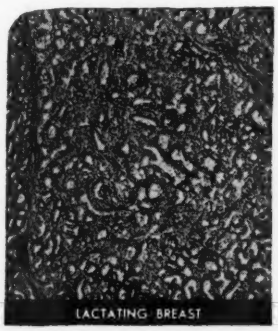
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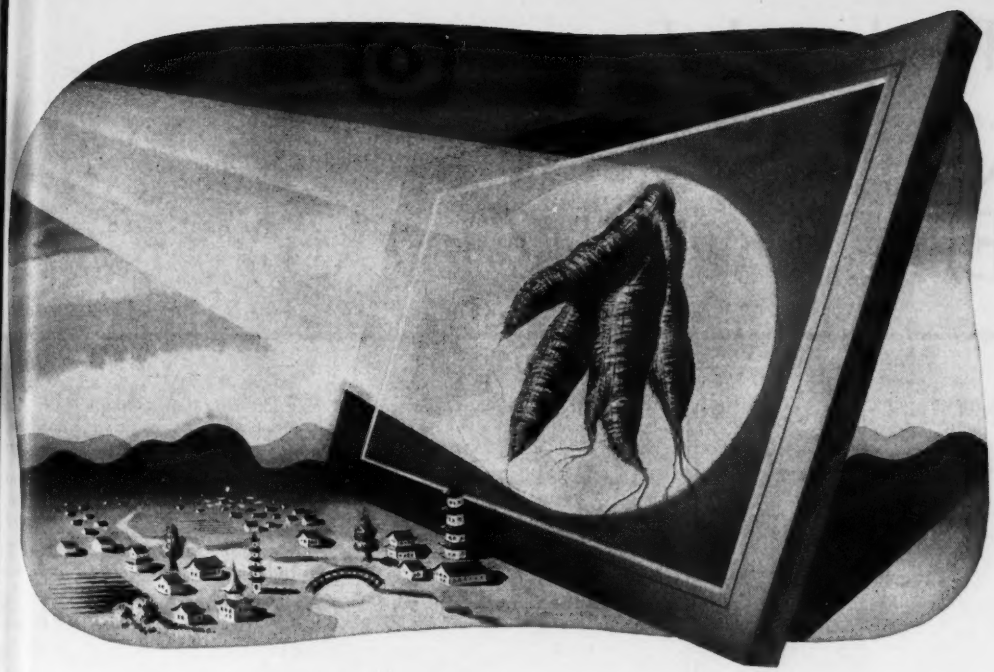

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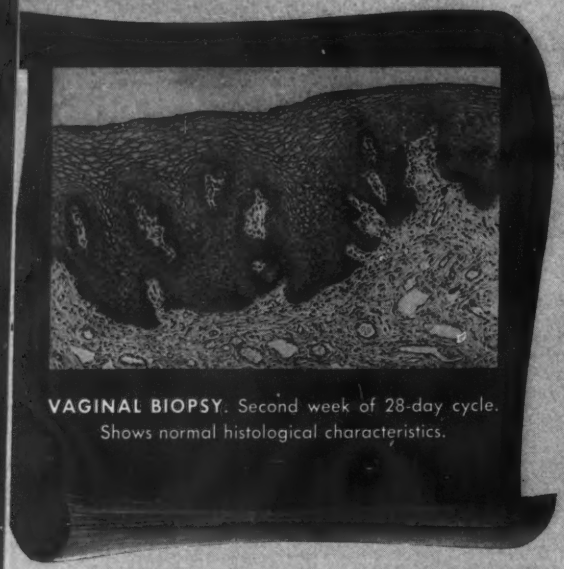

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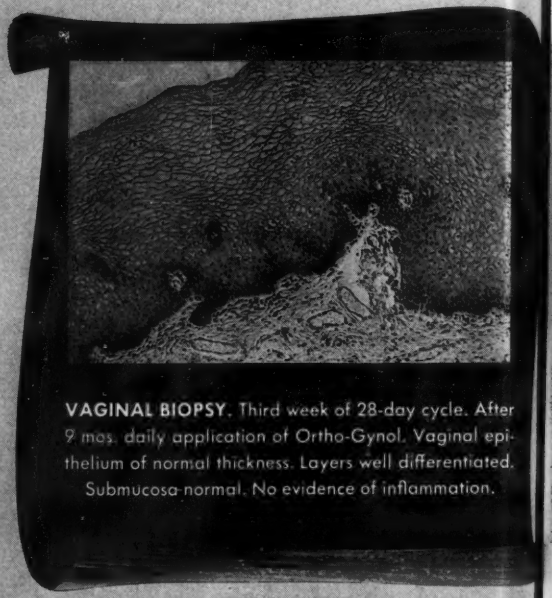

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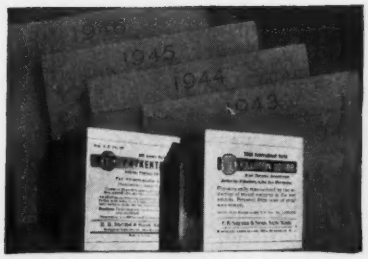

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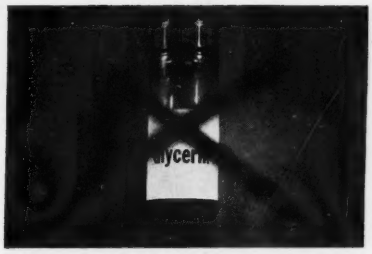

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